Genetically engineered crops, glyphosate and the deterioration of health in the United States of America

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Abstract

A huge increase in the incidence and prevalence of chronic diseases has been reported in the United States (US) over the last 20 years. Similar increas es have been seen globally. The herbicide glyphosate was introduced in 1974 and its use is ac celerating with the advent of herbicide-tolerant genetically engineered (GE) crops. Evidence is moun ting that glyphosate interferes with many metabolic processes in plants and animals and glyph osate residues have been detected in both. Glyphosate disrupts the endocrine system and the ba lance of gut bacteria, it damages DNA and is a driver of mutations that lead to cancer.

In the present study, US government databases were searched for GE crop data, glyphosate application data and disease epidemiological data. Correlation analyses were then performed on a total of 22 diseases in these time-series data sets . The Pearson correlation coefficients are highly significant ($< 10^{-5}$) between glyphosate applications and hypertension (R = 0.923), stroke (R = 0.925), diabetes prevalence (R = 0.971), diabetes incidence (R = 0.935), obesity (R = 0.962), lipoprotein metabolism disorder (R = 0.973), Alzheimer's (R = 0.917), senile dementia (R = 0.994), Parkinson's (R = 0.875), multiple sclerosis (R = 0.828), autism (R = 0.989), inflammatory bowel disease (R = 0.938), intestinal infections (R = 0.974), end stage renal disease (R = 0.975), acute kidney failure (R = 0.978), cancers of the thyroid (R = 0.988), liver (R = 0.960), bladder (R = 0.981), pancreas (R = 0.918), kidney (R = 0.973) and myeloid leukaemia (R = 0.878).

The Pearson correlation coefficients are highly sig nificant ($< 10^{-4}$) between the percentage of GE corn and soy planted in the US and hypertension (R = 0.961), stroke (R = 0.983), diabetes prevalence (R = 0.983), diabetes incidence (R = 0.955), obesity (R = 0.962), lipoprotein metabolism disorder (R = 0.955), Alzheimer's (R = 0.937), Parkinson's (R = 0.952), multiple sclerosis (R = 0.876), hepatitis C (R = 0.946), end stage renal disease (R = 0.958), acut e kidney failure (R = 0.967), cancers of the thyroi d (R = 0.938), liver (R = 0.911), bladder (R = 0.945) , pancreas (R = 0.841), kidney (R = 0.940) and myeloid leukaemia (R = 0.889). The significance and strength of the correlations show that the effects of glyphosate and GE crops on human health should be further investigated.

Introduction

Within the last 20 years there has been an alarming increase in serious illnesses in the US, along with a marked decrease in life expectancy (Bezruchka, 20   12). The Centers for Disease Control and Prevention (CDC) estimates that the cost of diabete   s and diabetes-related treatment was approximately $116 billion dollars in 2007. Estimated costs related to obesity were $147 billion in 2008 and cardiovascular diseases and stroke were $475.3   billion in 2009. Health care expenditures in the US totaled 2.2 trillion dollars in 2007 (CDC, 2013a   ). The onset of serious illness is appearing in increasingly younger cohorts. The US leads the worl d in the increase in deaths due to neurological diseases between 1979-81 and 2004-06 for the 55-65   age group (Pritchard et al., 2013). These mental disorder deaths are more typical of the over 65 age group. There have been similar findings for obesity, asthma, behavior and learning problems, an d chronic disease in children and young adults (Van Cleave et al., 2010). Type II diabetes in yout   h is being called an epidemic (Rosenbloom et al., 1999). The rate of chronic disease in the entire US   population has been dramatically increasing with an estimated 25% of the US population suffering fro   m multiple chronic diseases   (Autoimmunity Research Foundation, 2012). These findings suggest   environmental triggers rather than genetic or age-related causes.

During this same time period, there has been an exp   onential increase in the amount of glyphosate applied to food crops and in the percentage of GE f   ood crops planted (Benbrook, 2012). We undertook a study to see if correlations existed be   tween the rise of GE crops, the associated glyphosate use and the rise in chronic disease in the US.

Genetic engineering

To genetically modify a plant for herbicide toleran ce, genes are identified which convey tolerance of the active chemical in the herbicide to the organis   m. In the case of glyphosate, glyphosate-tolerant genes were isolated from a strain of *Agrobacterium*. These were inserted into the genome of the plant via a multi-step process resulting in a plant that   can withstand the direct application of the herbici de. Genetic modification is also utilised for developing insect resistant plants by using insecticidal pro teins from *Bacillus thuringiensis*, or Bt toxin. The promoter used to drive the expression of the foreign genes is generally the 35S promoter from the Cauliflower   Mosaic Virus (CaMV). Not only are the virus and bacteria genes themselves potentially harmful (Ho,   2013; Ewen & Pusztai, 1999), but the plants are sprayed directly with herbicides. The herbicide-tol erant plants absorb the poisons and humans and domestic animals eat them.

The GMO industry claims that genetic engineering is   no different than plant hybridisation, which has been practiced for centuries (FDA, 1992). It is the   reason they gave, which the US Food and Drug Administration (FDA) accepted, for not having to su bmit GE food to rigorous safety testing to obtain FDA approval. This distortion of the facts needs to be corrected.   One critical issue is that multiple genes are being transferred across taxonomical king   doms in ways that do not occur by natural breeding methods (Bohn et al., 2014).

All living things are classified according to a ran king system that starts with species and sub specie s. Closely related species are grouped together under   a rank that is called a genus. Closely related genera are grouped together under the rank of family. There are seven ranks. Starting with the highest they are: kingdom, phylum or division, class, order, family, genus, species.

Plants, animals, fungi, viruses and bacteria belong to separate kingdoms. Natural inter-breeding can take place between some species that belong to the   same genus and very occasionally between species of different genera. However, species that belong to different families do not inter-breed and definitely species that belong to different kingdoms such as plants, animals, fungi, bacteria and viruses do not inter-breed in nature. Plants, for example, do not inter-breed with animals, bacteria or viruse s. Genetic engineering allows for the transfer of gene s between kingdoms in a way that does not occur naturally.

The other great misconception is that only one gene with the desired trait is inserted. At this stage, science is not sophisticated enough to insert a sin gle gene and get it to work. To overcome this problem, scientists have to combine the gene with t he desired trait (such as herbicide tolerance or pesticide production) with other genes that will ma ke it work, such as promoter genes and marker genes. The result is a complex construction of tran sgenes that can come from bacterial, viral, fish, plant and other sources. This is completely different from natural hybridisation.

The stance taken by Monsanto, Dow, Bayer and the other purveyors of both chemicals and genetically engineered seeds is that GE food is "substantially equivalent" to non-GE products. According to the US FDA, "the substances expected to become components of fo od as a result of genetic modification of a plant will be the same as or substantially sim ilar to substances commonly found in food, such as proteins, fats and oils, and carbohydrates" (FDA, 1 992, Section I). The FDA maintains that it is up to the biotech companies that manufacture GE seeds to research and determine the safety of their products.

But Bohn et al. (2014) were able to discriminate be tween organic, conventional and GE soybeans without exception, based on vitamin, fat and protei n content. Furthermore, they were able to distinguish GE soybeans from both conventional and organic by their glyphosate and AMPA (glyphosate degradation product) residues, as well as substantial non-equivalence in numerous compositional characteristics of soybeans. The rese archers stated, "Using 35 different nutritional and elemental variables to characterise each soy sample , we were able to discriminate GM, conventional and organic soybeans without exception, demonstrating 'substantial non-equivalence' in compositional characteristics for 'ready-to-market' soybeans" (p. 207).

Exponentially increasing use of glyphosate world-wide
Since glyphosate was introduced in 1974 as the acti ve ingredient in Roundup® it has become the most widely used herbicide for urban, industrial, f orest and farm use (Monsanto, 2010). Pre-harvest application of glyphosate to wheat and barley as a desiccant was suggested as early as 1980, and its use as a drying or ripening agent 7-10 days before harvest has since become routine. It is now used on grain crops, rice, seeds, dried beans and peas, sugar cane and sweet potatoes (Monsanto, 2010; Orgeron, 2012; Orson & Davies, 2007). According to the Canadian Pulse Growers Association (PGA pamphlet, 2012), "Desiccants are used worldwide by growers who are producing crops that require 'drying down' to create uniformity of plant materia l at harvest. These products may also assist in pre - harvest weed control. In Canada, products such as d iquat (Reglone) and glyphosate (Roundup) have been used as desiccants in pulse crops in the past, and there are new products on the way." In 2012, 98% of spring wheat, 99% of durum wheat and 61% of winter wheat were treated with glyphosate or glyphosate salts in the US (USDA:NASS, 2013c). The glyphosate plots in this study include all formulations of glyphosate.

Monsanto, the manufacturer of Roundup®, states, "Si nce its discovery in the early 1970's the unique herbicidal active ingredient glyphosate has become the world's most widely used herbicide because it is efficacious, economical and environmentally beni gn. These properties have enabled a plethora of uses which continue to expand to this day providing excellent weed control both in agricultural and non-crop uses to benefit mankind and the environmen t. Glyphosate has an excellent safety profile to operators, the public and the environment. ... It i s approved for weed control in amenity, industrial, forestry and aquatic areas. Roundup Pro Biactive an d ProBiactive 450 can be used at any time of the year as long as weeds are green and actively growing" (Monsanto, 2010, p.1).

The Monsanto document outlines use areas including vegetation control on agricultural land, on GE Roundup Ready Crops and on non-agricultural land. B y 2006, glyphosate became used routinely for both agricultural and non-agricultural weed control and pre-harvest treatment. Since 1995, glyphosate use has rapidly increased with the planting of GE g lyphosate-tolerant crops. Glyphosate and its degradation product, aminomethylphosphonic acid (AMPA) have been detected in air (Majewski et al., 2014, Chang et al., 2011), rain (Scribner et al., 2 007, Majewski, 2014), groundwater (Scribner, 2007), surface water (Chang, 2011; Scribner, 2007; Coupe e t al., 2012), soil (Scribner, 2007) and sea water (Mercurio et al., 2014). These studies show that gl yphosate and AMPA persist in the soil and water, and the amounts detected are increasing over time w ith increasing agricultural use. Chang et al. (2011) reported that glyphosate was frequently dete cted in water, rain and air in the Mississippi Rive r basin with concentrations as high as 2.5 µg/L in agricultural areas in Mississippi and Iowa.

Because glyphosate is in air, water and food, human s are likely to be accumulating it in low doses over time. Glyphosate residues of up to 4.4 parts p er million (ppm) have been detected in stems, leaves and beans of glyphosate-resistant soy, indic ating uptake of the herbicide into plant tissue

(Arregui et al., 2004). Reports from Germany of gly phosate in the urine of dairy cows (Kruger et al., 2013b), rabbits and humans (Kruger et al., 2014) ra nged from 10-35 ppm. According to the study (Kruger, 2014, p. 212), "Chronically ill humans had significantly higher glyphosate residues in urine than healthy humans." Furthermore, the cows were di ssected and glyphosate residues in the tissues of the kidney, liver, lung, spleen, muscles and int estines were comparable to that found in the urine. This means that the glyphosate is not being passed through the urine without affecting the organism and that meat and dairy are an additional source of dietary glyphosate for humans.

Industry and lobbyists claim that GE crops reduce the amount of pesticides used on crops, resulting in a more sustainable agriculture. This has proved not to be the case. Since the introduction of GE seeds in 1996 the amount of glyphosate used on crops in t he US has increased from 27 million pounds in 1996 to 250 million pounds in 2009 (US Geological S urvey pesticide use maps, 2013). Charles Benbrook (2012) showed that there was a 527 million pound (239 million kilogram) increase in herbicide use in the United States between 1996 and 2011. Furthermore, Benbrook states that the spread of glyphosate-resistant weeds has brought ab out substantial increases in the number and volume of herbicides applied. This has led to genet ically engineered forms of corn and soybeans tolerant of 2,4-D, which he predicts will drive herbicide usage up by approximately 50% more.

In the US, glyphosate residues allowed in food are some of the highest in the world. In July of 2013 the Environmental Protection Agency (EPA, 2013) rai sed the maximum allowable residues of glyphosate. An abbreviated list is provided in Table 1 and Table 2.

Table 1. Glyphosate residues allowed in food from crops (EPA, 2013).

Crop	Maximum residue allowance for glyphosate (ppm)
Beet, sugar, dried pulp	25
Beet, sugar, roots	10
Beet, sugar, tops	10
Canola, seed	20
Corn, sweet, kernel plus cob	3.5
Grain, cereal, group 15	30
Oilseeds, except canola	40
Pea, dry	8
Peppermint, tops	200
Quinoa, grain	5
Shellfish	3
Soybean, seed	20
Spice subgroup 19B	7
Sugarcane, cane	2
Sugarcane, molasses	30
Sweet potatoes	3
Vegetable, legume, group 6 except soybean and dry pea	5

Table 2. Glyphosate residues allowed in livestock feed (EPA, 2013).

Animal feeds	Maximum residue allowance for glyphosate (ppm)
Grass, forage, fodder and hay, group 17	300
Grain, cereal, forage, fodder and straw	100
Soybean, forage	100
Soybean, hay	200
Soybean, hulls	120
Cattle, meat byproducts	5

Glyphosate and disease
The connection between glyphosate and chronic disea se has been outlined in a recent review paper by Samsel & Seneff (2013a). The authors show how gl yphosate disrupts the metabolic process by interfering with the Cytochrome P450 (CYP) pathways . The CYP is known as a super-family of enzymes that are present in most tissues of the bod y. They are responsible for around 75% of the reactions involved in drug metabolism and the oxida tion of organic molecules. According to the authors, "glyphosate enhances the damaging effects of other food borne chemical residues and environmental toxins. Negative impact on the body i s insidious and manifests slowly over time as inflammation damages cellular systems throughout th e body. Here, we show how interference with CYP enzymes acts synergistically with disruption of the biosynthesis of aromatic amino acids by gut bacteria, as well as impairment in serum sulfate tr ansport. Consequences are most of the diseases

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and conditions associated with a Western diet, whic   h include gastrointestinal disorders, obesity, diabetes, heart disease, depression, autism, infert ility, cancer and Alzheimer's disease. We explain the documented effects of glyphosate and its ability to induce disease, and we show that glyphosate is the 'textbook example' of exogenous semiotic entropy: the disruption of homeostasis by environmental toxins" (p. 1416).

Séralini et al. (2011) reviewed 19 studies of anima ls fed with GE soy and corn. The studies covered more than 80% of the GE varieties that are widely c   ultivated around the world. Their review found significant levels of negative effects to the kidneys and livers of the animals that ingested GE feed.

In another review article, Samsel & Seneff (2013b) point out that glyphosate is patented as a biocide and, as such, it kills the beneficial bacteria in o ur gut, leading to the steep rise in intestinal dis eases. This has also been reported in the microbiota of ho   rses and cows (Kruger, 2013a) and poultry (Shehata et al., 2012) where it was found that, "hi   ghly pathogenic bacteria as *Salmonella Entritidis*, *Salmonella Gallinarum*, *Salmonella Typhimurium*, *Clostridium perfringens* and *Clostridium botulinum* are highly resistant to glyphosate. However, most of beneficial bacteria such as *Enterococcus faecalis*, *Enterococcus faecium*, *Bacillus badius*, *Bifidobacterium adolescentis* and *Lacto-bacillus* spp. were found to be moderate to highly susceptible" (p. 350   ). The authors postulate that glyphosate is associated with the increase in   *C. botulinum* -mediated diseases in these domestic farm animals. Carman et al. (2013) reported that a diet of GE cor   n and soy was associated with stomach inflammation in pigs.

In 2012, Antoniou et al. published a review of the   evidence on the teratogenicity and reproductive toxicity of glyphosate on vertebrates. Gasnier et a l. (2009) published evidence that glyphosate-based herbicides are endocrine disruptors in human cells. They reported toxic effects to liver cells at 5 pp m and endocrine disrupting actions starting at 0.5 pp m. They concluded that glyphosate damages DNA in human cells.   Subsequent studies have also shown that glyphosate   is an endocrine disruptor (Paganelli et al., 2010; Antoniou et al., 2012). A more recent study showed that glyphosate causes the multiplication of estrogen sensitive human breast cancer cells, which further confirms that it acts as an endocrine disruptor (Thongprakaisang et al., 2013).

An endocrine disruptor is a chemical that either mi   mics or blocks hormones and disrupts the body's normal functions. This disruption can happen throug   h altering normal hormone levels, halting or stimulating the production of hormones, or interact ing directly with the organ the hormone was meant to regulate. Because hormones work at very small do   ses, endocrine disruption can occur from low-dose exposure to hormonally active chemicals (Vande   nberg et al., 2012). Threshold doses of pesticides are set based on toxicology studies assu ming the response is linear. But the response is not only non-linear, it is also dependent on the ho rmone level in the body at any given time. The meta study on endocrine disruption by the World Health O rganisation and the United Nations Environment Program clearly makes this point (Bergman et al., 2   013, p. 19): "Endocrine disruptors produce non linear dose responses both in vitro and in vivo; these non linear dose responses can be quite complex and often include non-monotonic dose responses. The   y can be due to a variety of mechanisms; because endogenous hormone levels fluctuate, no thr   eshold can be assumed." Consequently,   low doses over long periods of time may lead to very serious illnesses.

Endocrine disruptors can increase or decrease hormo   ne production, imitate hormones or even transform one hormone into another. Endocrine disru   ptors can also tell cells to die prematurely, compete with essential nutrients and build up in ho   rmone-producing organs. These imbalances and malfunctions of the endocrine system can lead to di   abetes, hypertension, obesity, kidney disease, cancer (breast, prostate, liver, brain, thyroid, no   n-Hodgkin's lymphoma) (Marc et al., 2004; Thongprakaisang et al., 2013), osteoporosis, Cushin   g's syndrome, hypo- and hyperthyroidism, infertility, birth defects, erectile dysfunction (S   oto & Sonnenschein, 2010), sexual development problems and neurological disorders such as: learni ng disabilities, attention deficit disorder (ADD) (de Cock et al., 2012), autism (Schulkin, 2007), dement ia (Ghosh, 2010), Alzheimer's (Merlo et al., 2010), Parkinson's and schizophrenia (MacSweeney et al., 1   978). Endocrine disruptors are especially damaging to organisms undergoing hormonal changes: fetuses, babies, children, adolescents and the elderly (Bergman et al., 2013).

Given that glyphosate disrupts gut bacteria balance , the metabolic process, the uptake of nutrients, the endocrine system, and damages DNA, it seemed li kely that there would be correlations between the increase of these diseases and the exponential increase in the use of glyphosate, particularly wit h the advent of glyphosate-resistant food crops. To t his end, we searched for epidemiological disease data, along with pesticide use on crops and the per   centage of GE crops planted since first being

introduced in 1995. These were plotted and Pearson   correlation coefficients were calculated. These data, provided by the US government, are readily available on the internet.


Methods

United States Government databases were searched fo r GE crop data, glyphosate application data and disease epidemiological data. Correlation analy   ses were then performed on these time-series data sets.

Crop data
The United States Department of Agriculture Nationa   l Agricultural Statistics Service (USDA:NASS) maintains a database of US crops. Every year they r   andomly select fields of certain crops and send surveys to the persons who manage those fields. Amo ng other things, they ask what herbicides were used, the application rate, how many times was it a   pplied, and whether or not the field was planted with a GE variety. Surveys are only sent to the sta   tes that are the major producers of a given crop, usually accounting for about 90% of the total US ac   reage planted in that crop. They then perform a statistical analysis and report the total acreage p   lanted, the percentage of acres that are GE, the Percentage of Acres Treated (PAT) with each herbici de for that crop and the application rate per acre per year. One can then calculate the total amount o f an herbicide that was applied to that crop in the survey states for that year.

Data files from the USDA containing the information   for GE varieties are available from 2000-2013 (USDA:NASS 2013a), but only corn, cotton and soy ar e tracked. Data for 1996-1999 were obtained from a USDA agricultural report (Fernandez-Cornejo & McBride, 2002). The survey states accounted for 85-90% of all corn, cotton and soy grown in the   US. Sampling errors for the percentage of GE crops planted are given as 1-2%, varying by year an d crop. The increase in the adoption of GE crops in the US from 1996-2010 is shown in Figure 1.

Data files containing the information for herbicide   applications are available from 1990-2012 (USDA:NASS 2013b). Sampling errors (reported as sta ndard errors) are small (<5%) in both the PAT and the application rate if the PAT is greater than   50%. Sampling errors are 5-10% if the PAT is between 10-50%, while the sampling errors are 10-10 0% if the PAT is <10%. We extracted the data for glyphosate applications to corn, cotton and soy . Data for cotton was not included in these results because, except for cottonseed oil in food and cott onseed meal in animal food, cotton is not generally considered a food crop. Though the manufacturers cl   aim that there are no GE content or traits in processed foods (like oil), it has been reported th at glyphosate residues up to 0.350 ppm have been detected in refined soy oil (GEAC, 2006).
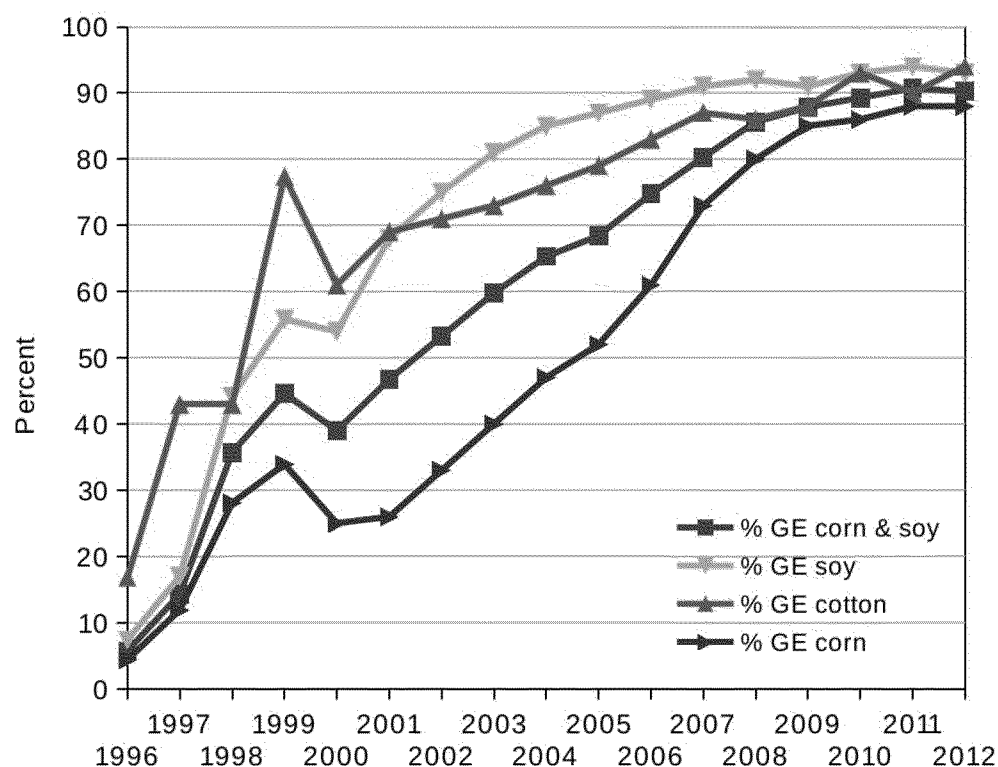
Figure 1. Adoption of GE crops in US.

From 1990-2002, glyphosate data were available for all three crops, but beginning in 2003 data were not collected for all three crops in any given year . Data on the application rates were interpolated f or the missing years by plotting and calculating a bes t fit curve. Results for the application rates for soy and corn are shown in Figures 2 and 3. Because the PAT was relatively small prior to about 1995, the sampling errors are much larger for pre-1995 data, more so for corn than for soy. Also, data were not missing until 2003 for soy and 2004 for corn. For t hese reasons, the interpolated curves begin in 1996 for soy and 1997 for corn in Figures 2 and 3.

To calculate the amount of glyphosate applied, it w as also necessary to interpolate the PAT for both corn and soy. This was easier because they followed almost exactly the curves for the percentage of acres planted in GE crops. GE soy crops are only he rbicide tolerant (HT), which nicely tracked with the PAT for glyphosate, as shown in Figure 4. GE cor n crops can be either insecticide resistant (Bt) or HT or both (stacked). The HT and stacked trait perc entages, reported separately in the USDA files for corn, were plotted with the PAT for glyphosate as sh own in Figure 5.
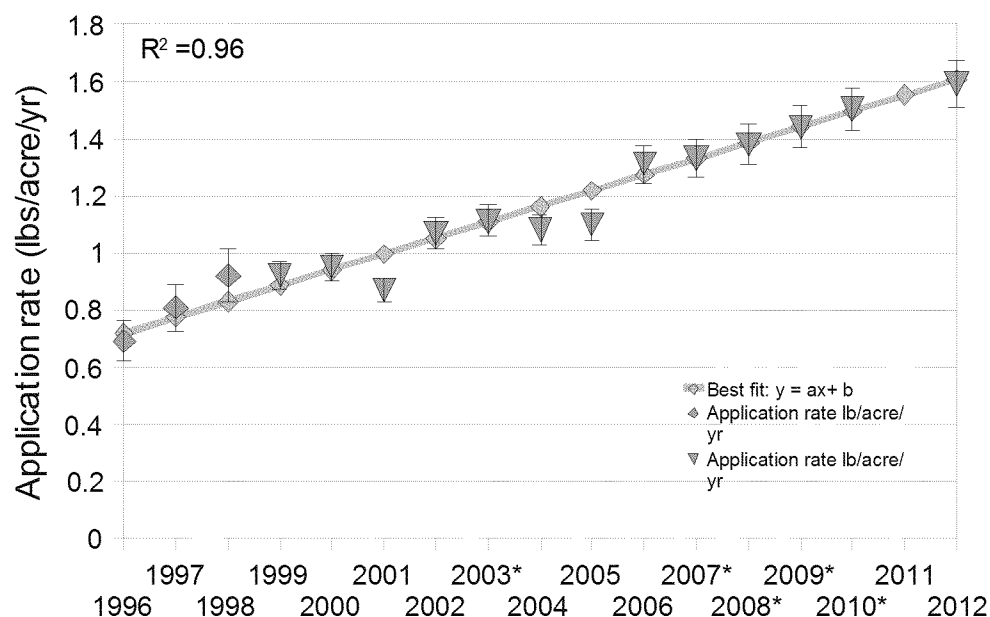
Figure 2. Application rate of glyphosate on soy. Best fit y=ax+b, interpolated values indicated with * next to the year. Error bars are from reported standard error from USDA. The residual standard error from the linear fit is 0.07 lb/acre/year.
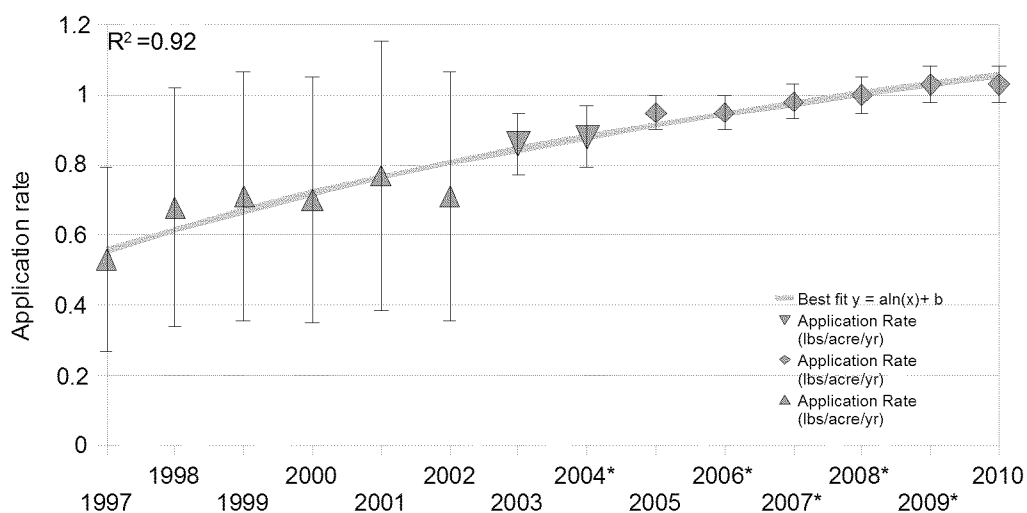

Figure 3. Application rate of glyphosate on corn. Best fit y=a ln(x)+b, interpolated values indicated with * next to the year. Error bars are from reported standard error from USDA. The residual standard error from the linear fit is 0.06 lb/acre/year. Large errors for the earlier years are because of the smaller PAT with glyphosate.
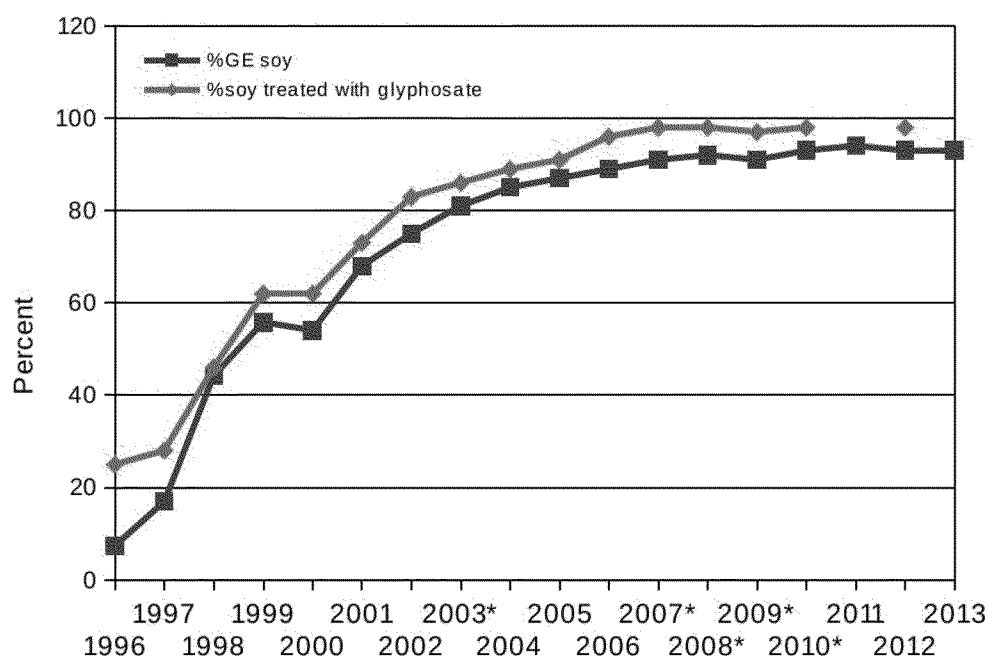
Figure 4. Percentage of GE soy crops planted and PAT with glyphosate. Interpolated values are indicated with an * next to the year. Data were not available for glyphosate applications to soy from 2007-2011. Data were only used through 2010; therefore the data point at 2011 was not interpolated. Data for 2012 are shown for reference.
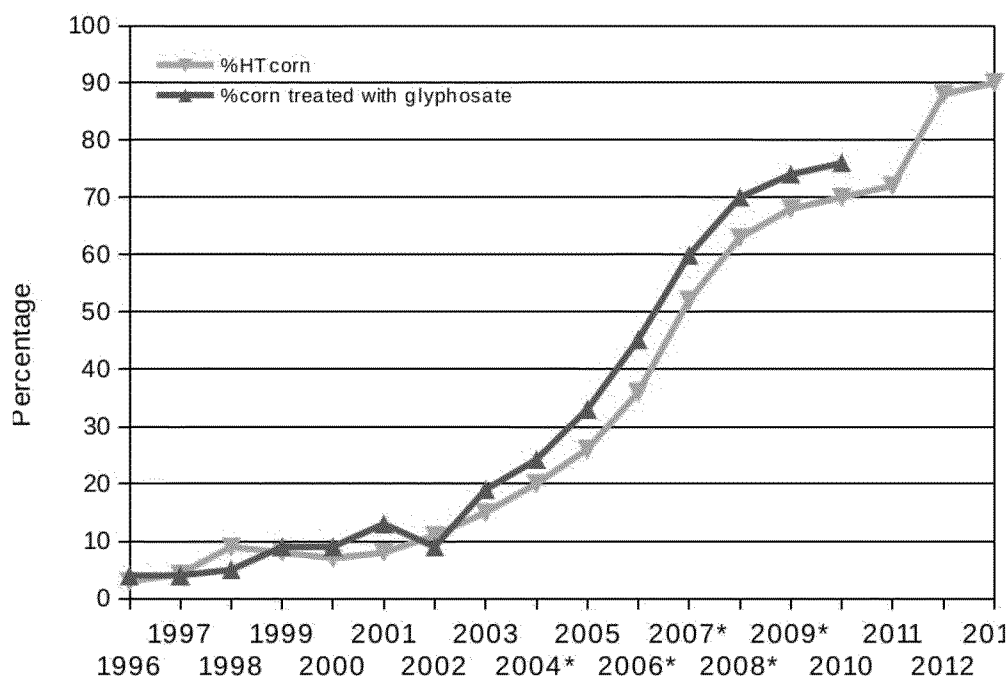
Figure 5. Percent GE corn crops and PAT with glyphosate; interpolated values indicated with *.

From these data, along with the total acreage plant ed in the survey states, the amount of glyphosate (in tons) applied to corn and soy crops in those st ates for each year from 1990-2010 was calculated and is shown in Figure 6. The calculation is: appli   cation rate (lbs/acre/year)*PAT/100*total acres planted. The contribution of glyphosate on soy is a bout twice that for corn. While both corn and soy are major US food crops (75-80 million acres plante d annually), GE corn was more slowly adopted (Figure 1) and some of the earlier GE corn is Bt on ly. The curve for glyphosate applied to all three crops is included only to show that the shape of th e curve is unchanged, so it is doubtful there would have been much change in the results had cotton been included.
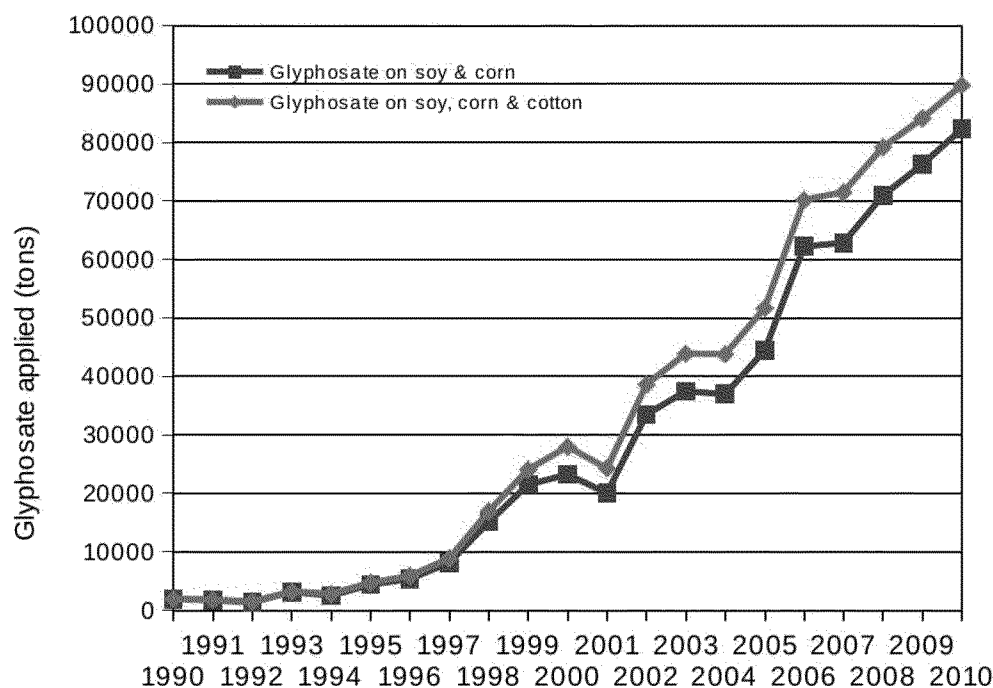
Figure 6. Glyphosate applied to corn, cotton and soy crops in the surveyed states. Standard errors (corn & soy): 2007-2010: 3-10%; 2000-2006: 7-16%; 1998-2000: 16-62%; 1992-1997: 16-100%; 1990-1991: 22-100%. Errors calculated from the USDA reported standard errors.

Epidemiological disease data

Databases were searched for epidemiological data on diseases that might have a correlation to glyphosate use and/or GE crop growth based on infor mation given in the introduction. The primary source for these data was the Centers for Disease C ontrol and Prevention (CDC). These data were plotted against the amount of glyphosate applied to corn and soy from Figure 6 and the total %GE corn and soy crops planted from Figure 1. The perce ntage of GE corn and soy planted is given by: (total estimated number of acres of GE soy + total estimated number of acres of GE corn)/(total estimated acres of soy + total estimated acres of c orn)x100, where the estimated numbers were obtained from the USDA as outlined above.

Statistical analyses

A statistical analysis was performed on each of the data sets. A standard analysis for correlating two sets of data is to calculate the Pearson correlatio n coefficients. The Pearson correlation coefficient is based on the linear least-squares formulation, whic h in turn is based on the assumption that each of the individual variables is normally distributed. A ll of the US government data, both crop data and disease data, were gathered from surveys and census data. These data were statistically analysed and the results reported as an average with an asso ciated error (standard deviation of the mean), indicating that normal distributions were assumed in the statistical methods used.

We generated scatter plots for each set of data (di sease vs. glyphosate applications and disease vs. percentage of GE crops) to determine whether or not the Pearson correlation method (i.e. linear least-squares method) was appropriate. The scatter plots showed a strong linear relationship between the two data sets in all cases. Plots of the residuals were checked to confirm homogeneity.

The Pearson's correlation coefficient, R, is a dete rmination of how closely correlated the two data se ts are, i.e., how close the scatter plot is to a line. For N pairs of (x, y) data, the correlation coefficient is given by $R = \sigma_{xy}/(\sigma_x \sigma_y)$ where σ_{xy} is the covariance, $\sigma_{xy} = /N \quad (x_i - \bar{x})(y_i - \bar{y})$ and σ_x and σ_y are the standard deviations of the x and y variables.

When the individual standard deviations are not kno wn, but calculated from the data sets themselves, the statistic $t = R\sqrt{(N-\quad)2(1-R^2)}$ can be used to test the claim that there is a posi tive correlation by calculating the probability that a value of R greater than or equal to that observed would have been

obtained if R were in fact 0 (the null hypothesis). If this prob ability, the P-value, is less than 5%, the correlation is deemed to be significant. If it is l ess than 1% it is described as highly significant. The probabilities obtained here are very small, so we m ay confidently reject the null hypothesis that R = 0. After verifying the accuracy of the results, we per formed the correlation calculations using the onlin e statistical package from the University of Amsterdam (UA, 2014).

Much of the CDC data is stored and retrieved accord ing to the International Classification of Disease (ICD) codes. These codes changed from 1998 to 1999, causing some concern that there would be a discontinuity in the graphs between those years due   to improper coding or added or subtracted categories. This only showed up in one graph, Alzhe imer's. It is unclear whether the jump in the data on this graph is real or an artefact from the code change.

Results and Discussion

The plots are loosely grouped into related disease   categories. If the disease data were linearly increasing prior to the 1990s, a linear trend line   was overlaid on the plot in green. The error bars o n the green trend lines are the residual standard err ors from the least squares fit. In some cases, the axes have been adjusted to better illustrate the co rrelation; otherwise the data are plotted as is. In all cases, the left vertical axis is the prevalence or   the rate of incidence or death from the disease. Th e right vertical axis is both the percentage of GE corn and soy planted and the amount (in 1,000 tons) of glyphosate applied to the corn and soy crops.
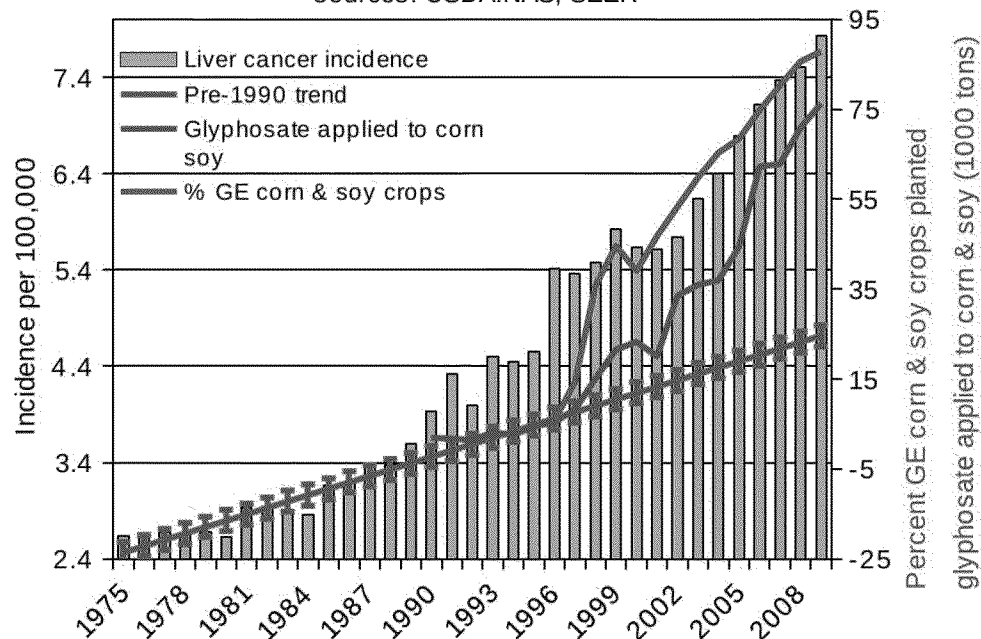
Correlations of cancers of the liver, kidney, bladd er, and thyroid with the planting of GE crops and glyphosate applications
Epidemiology data for cancer incidence were obtained from the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) database (Natio   nal Cancer Institute, 2013). Based on published reports on endocrine disruptors, we expected but did not find correlations for: non-Hodgkin's lymphoma (slightly rising), prostate (oscillating), testicular (slightly rising), colon (slightly decr easing) and breast (slightly decreasing) cancers. The decre   ase in breast cancer may be attributable to reduced use of hormone replacement therapy (Chlebowski, 2012).

We found strong correlations for cancers of the liv er, kidney, bladder/urinary and thyroid. Results ar e shown in Figures 7-10. Thyroid and bladder cancers   especially seem to track with the advent of GE crops and associated glyphosate applications. Thyro id cancer seems to affect females more, while males are more susceptible to liver and kidney canc   ers (not shown in graphs). We found weaker correlations between pancreatic cancer incidence (R = 0.84 with %GE crops & R = 0.92 with glyphosate applications) and deaths from acute myel oid leukaemia (R = 0.89 with %GE crops & R = 0.88 with glyphosate applications). Both of these p eaked in the 1980s, then decreased and are now rising again. Pancreatic cancer incidence began rising again in 1996 and myeloid leukaemia deaths in 1989.

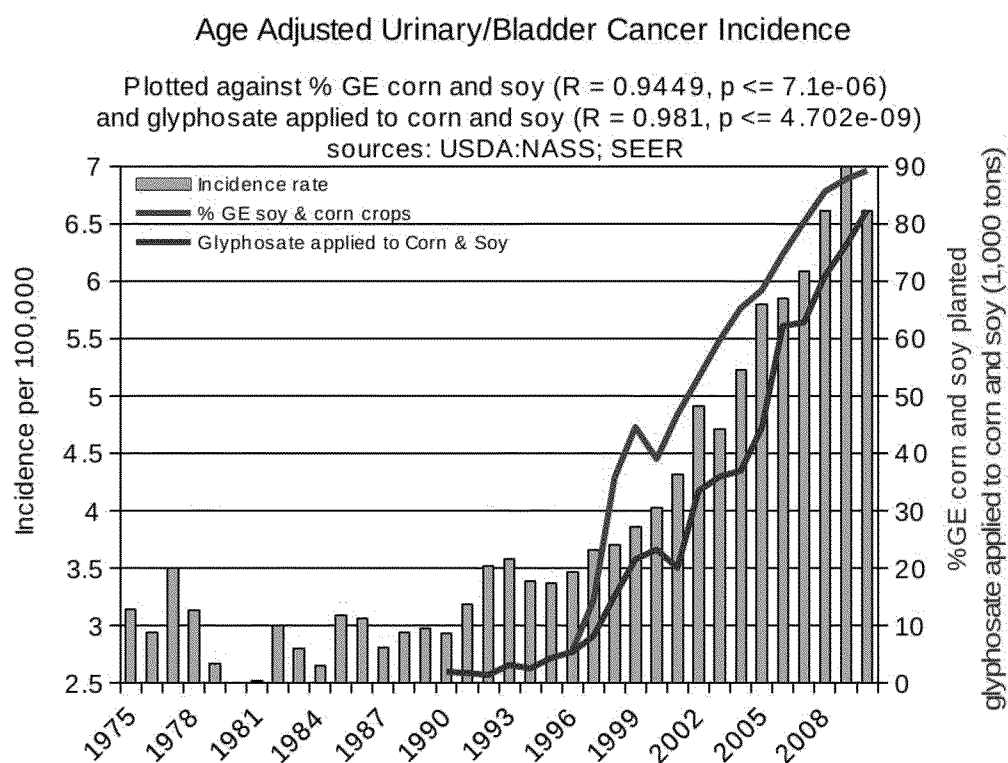**Figure 7. Correlation between age-adjusted liver cancer incidence and glyphosate applications and percentage of US corn and soy crops that are GE.**

Figure 8. Correlation between age-adjusted kidney cancer incidence and glyphosate applications and percentage of US corn and soy crops that are GE.
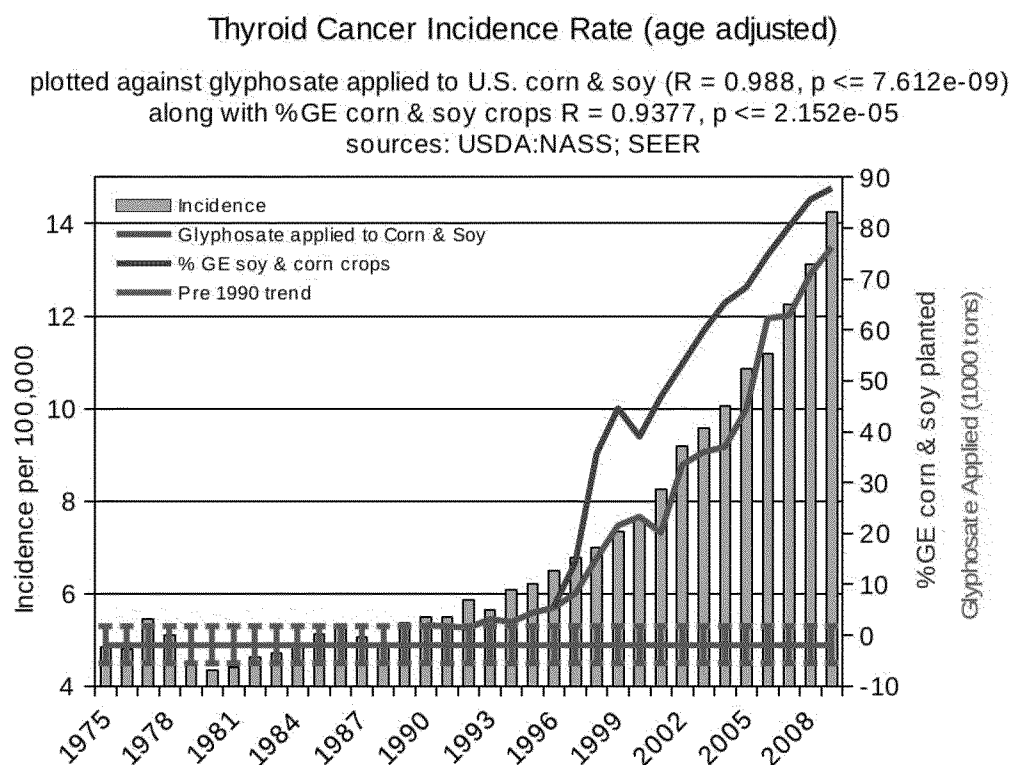
Age Adjusted Urinary/Bladder Cancer Incidence

Plotted against % GE corn and soy (R = 0.9449, p <= 7.1e-06)
and glyphosate applied to corn and soy (R = 0.981, p <= 4.702e-09)
sources: USDA:NASS; SEER

Figure 9. Correlation between age-adjusted bladder/urinary tract cancer and glyphosate applications and percentage of US corn and soy crops that are GE.

Thyroid Cancer Incidence Rate (age adjusted)

plotted against glyphosate applied to U.S. corn & soy (R = 0.988, p <= 7.612e-09)
along with %GE corn & soy crops R = 0.9377, p <= 2.152e-05
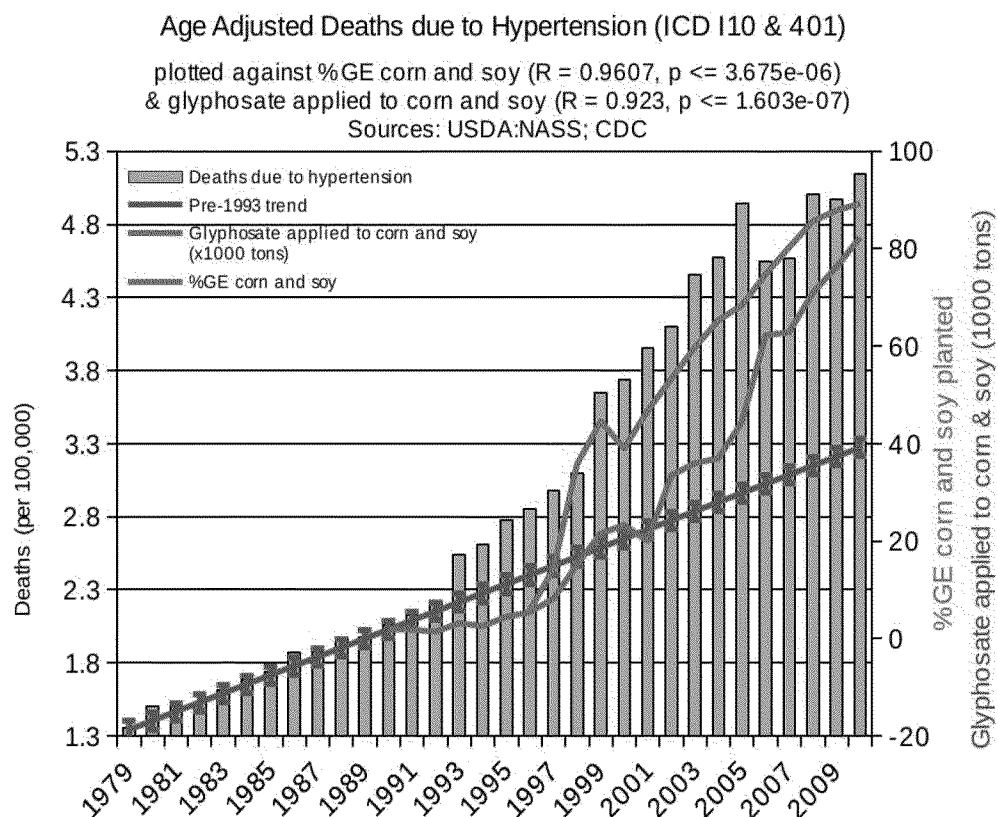sources: USDA:NASS; SEER

Figure 10. Correlation between age-adjusted thyroid cancer incidence and glyphosate applications and percentage of US corn and soy crops that are GE.

Correlations between hypertension and hemorrhagic s   trokes with the planting of GE crops and glyphosate applications
Correlations for deaths due to hypertension and hem   orrhagic stroke are shown in Figures 11 & 12.
Death data were obtained from the CDC mortality fil   es (CDC, 2013b).   Data for hypertensive heart disease suffered from a discontinuity between the years 1998 and 1999, most likely due to the change in ICD codes at that time (Joyner-Grantham, 2010).   After adjusting the latter data (multiplying by a

constant factor) to remove the discontinuity, we fo und R = 0.93 with glyphosate applications and R = 0.94 with %GE crops, but the results are not presen   ted here due to the necessary manipulation of those data.

Figure 11. Correlation between age-adjusted hypertension deaths and glyphosate applications and percentage of US corn and soy crops that are GE.
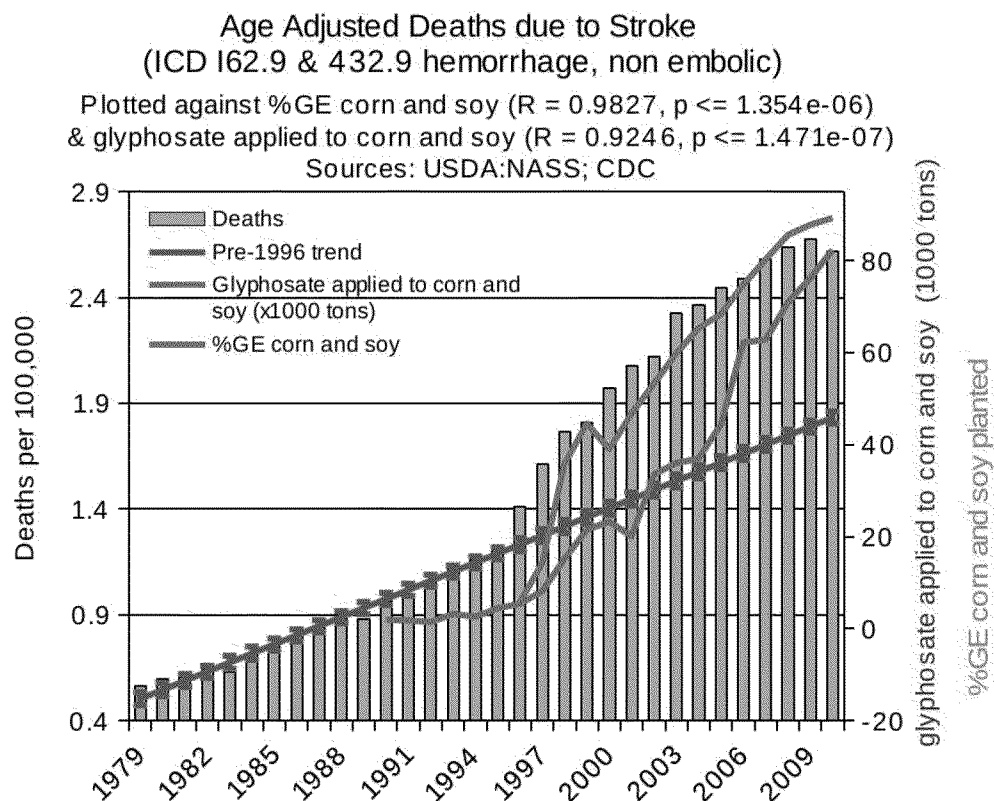
Figure 12. Correlation between age-adjusted hemorrhagic stroke deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Correlations of obesity, lipoprotein metabolism dis order and diabetes with the planting of GE crops and glyphosate applications

Epidemiological data for obesity deaths, lipoprotei   n metabolism (hyperlipidemia & hypercholesterolemia) disorder deaths, and diabetes incidence and prevalence also showed strong correlations with glyphosate use and GE crop growth . Death data were again obtained from the CDC mortality files (CDC, 2013b). Diabetes prevalence (CDC, 2013c) and incidence (CDC, 2013d) data were obtained from CDC National Center for Health Statistics. Results are shown in Figures 13-16.

According to the CDC, approximately one third of pe   ople with diabetes have not been diagnosed. Therefore, the National Health Interview Survey und erestimates the true incidence and prevalence of diabetes. Because diabetes and obesity are associat ed with sugar consumption, we present the per capita sweetener delivery for US consumption (USDA,   2013) in Figure 17. The majority of the sugar consumed is from corn, sugar beets and sugar cane. In 2011, 88% of the corn (USDA:NASS, 2013a) and 90% of sugar beets (ISAAA, 2011) planted in the   US were GE. Glyphosate is routinely used for sugar cane crop ripening and desiccation (Orgeron, 2012).

Hyperlipidemia is characterised by inflammation of   the pancreas (pancreatitis), abdominal pain, enlargement of the liver and spleen (hepatosplenome   galy), and small yellow skin lesions called eruptive xanthomas (Raphael, 1993; Berglund, 2012).   Diseases associated with secondary hyperlipidemias include obesity, diabetes mellitus   (type I and type II), hypothyroidism, Cushing's syndrome, chronic kidney disease, nephrotic syndrom e, and cholestatic disorder, a major risk factor for atherosclerosis and cardiovascular disease.

According to Samsel & Seneff (2013a) glyphosate disrupts the CYP enzymes that are heavily involved in producing bile acids. Ordinarily, the liver expo rts a lot of cholesterol as cholesterol sulfate int o the bile acids. This allows the digestive system to dig   est fats, which are then packaged up into the chylomicron with the cholesterol sulfate packed int   o its outer shell to deliver cholesterol to all the tissues. When the liver cannot make bile acids, it   is forced to divert the cholesterol into LDL, so th e LDL rises, resulting in hypercholesterolemia.

Furthermore, lipoprotein metabolism disorder has be   en associated with Alzheimer's (AD) and Parkinson's diseases (Merlo, 2010). According to Me   rlo, "Recent evidence suggests a strict link between metabolic disorders and AD. In the last dec   ade much attention has focused specifically on the connection between dysfunction of lipid metabol   ism and AD. Here we discuss aspects of lipid regulation, including changes in cholesterol levels   , function of apolipoproteins and leptin, and how these relate to AD pathogenesis. Despite the vast l   iterature available, many aspects still need clarification. Nevertheless, the route is already delineated to directly connect aspects of lipid regulation to AD" (p. 537).
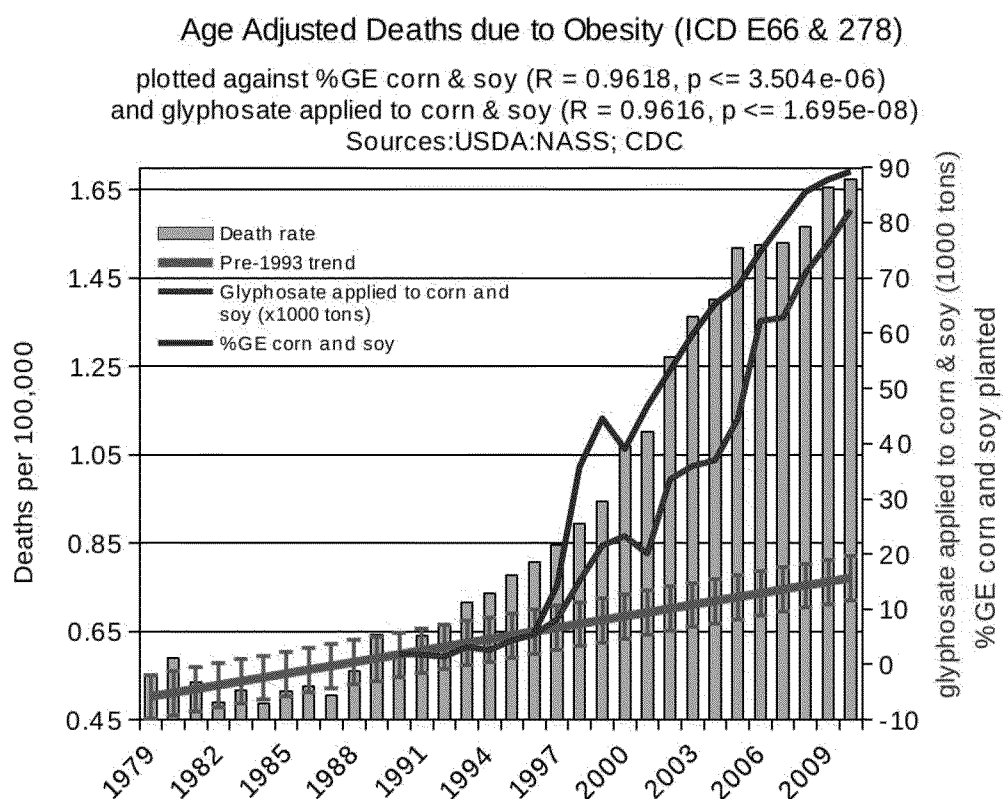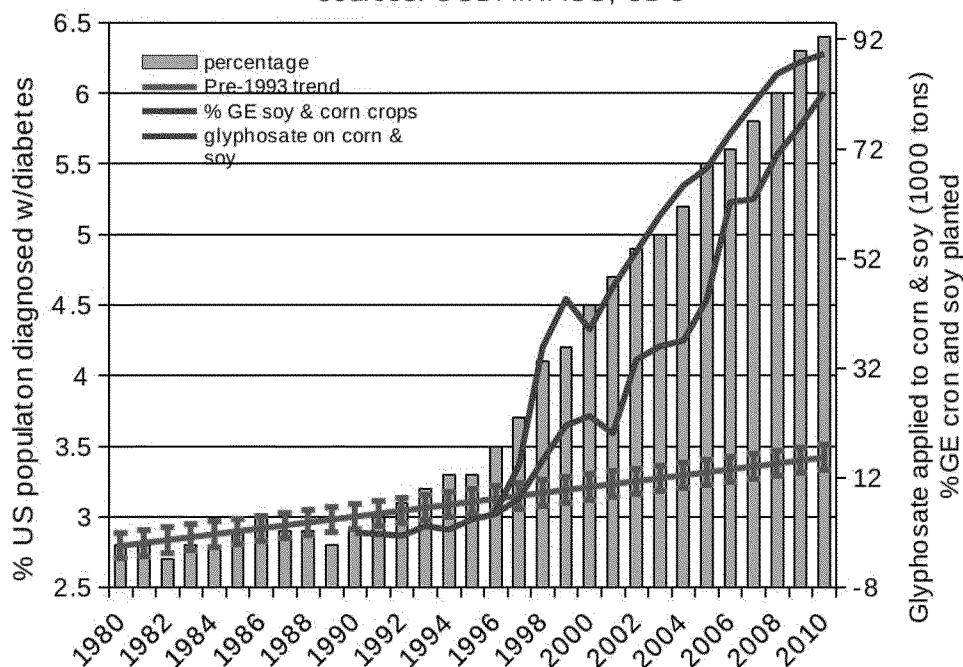
Figure 13. Correlation between age-adjusted obesity deaths and glyphosate applications and percentage of US corn and soy crops that are GE.
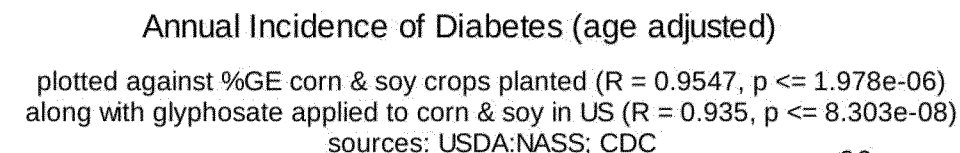
Figure 14. Correlation between age-adjusted diabetes incidence and glyphosate applications and percentage of US corn and soy crops that are GE.

Figure 15. Correlation between age-adjusted diabetes prevalence and glyphosate applications and percentage of US corn and soy crops that are GE.
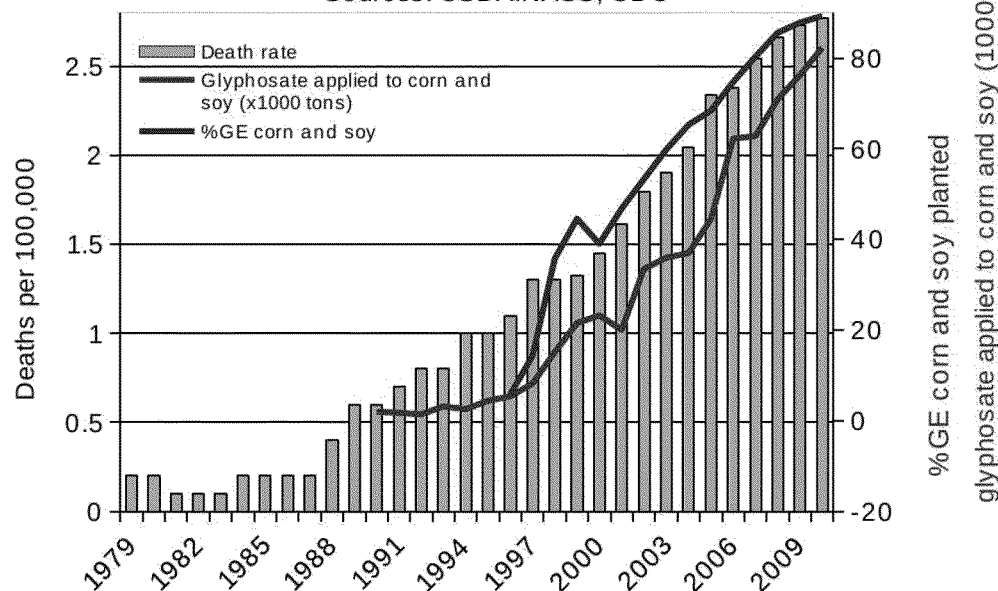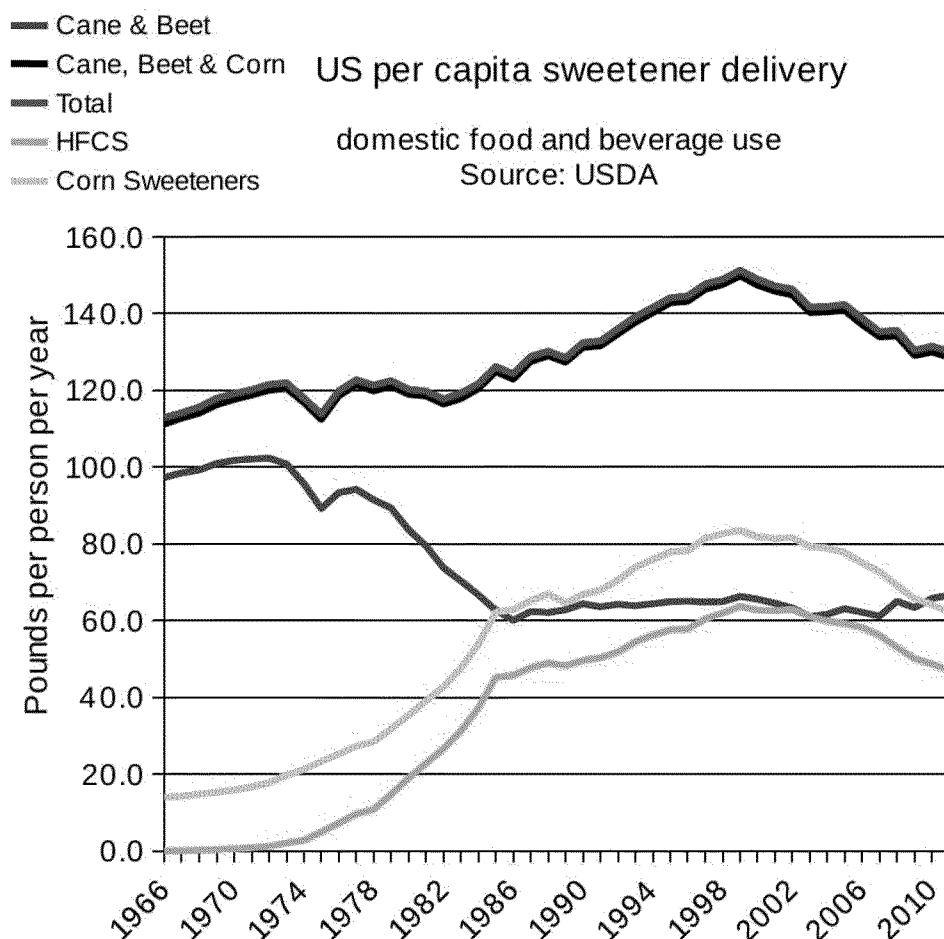

Figure 16. Correlation between age-adjusted lipoprotein disorder deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Figure 17. Sugar consumption in the US. The black line is sugar from cane, beet and corn combined; the red line is the total of all sources, including honey and syrups.
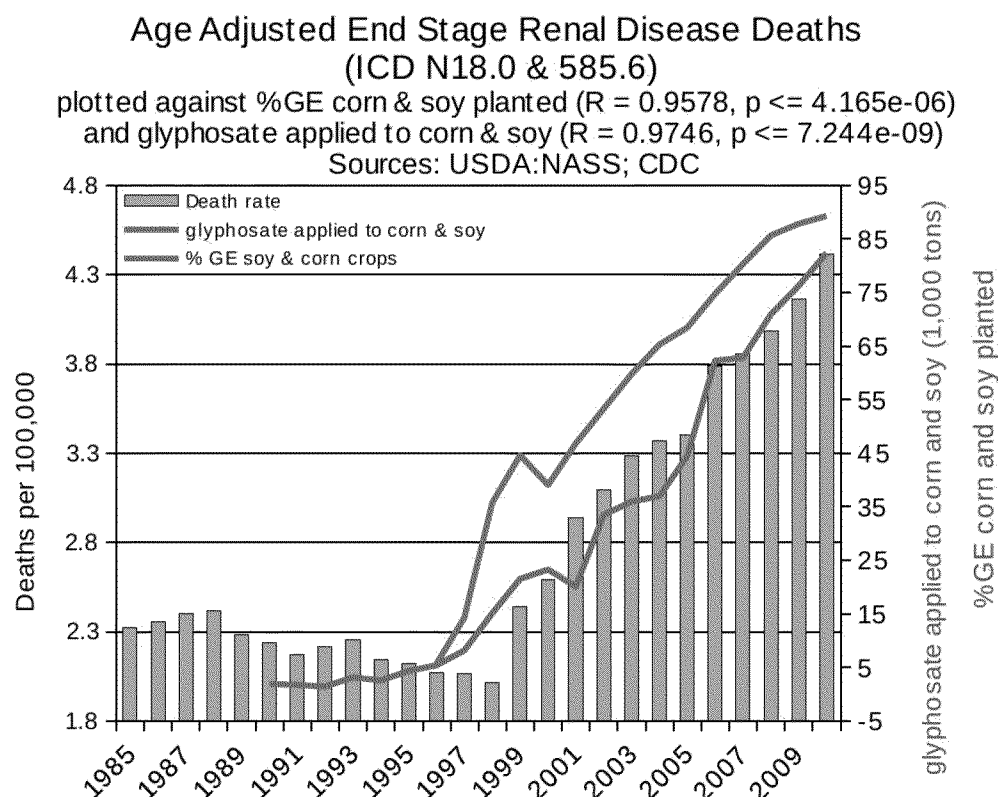
Correlations of renal failure with the planting of GE crops and glyphosate applications
Deaths from end stage renal disease (ESRD) and acut e renal failure showed strong correlations with glyphosate use and GE crop growth. Death data were   obtained from the CDC mortality files (CDC 2013b). Results are shown in Figures 18 and 19. Bot h of these have a peak in the mid-1980s, then decline and start rising again in the mid-1990s. Th e slight jump in ESRD deaths from 1998 to 1999 could be due to the ICD code changes at that time, but this was not apparent in the crude death rate data.
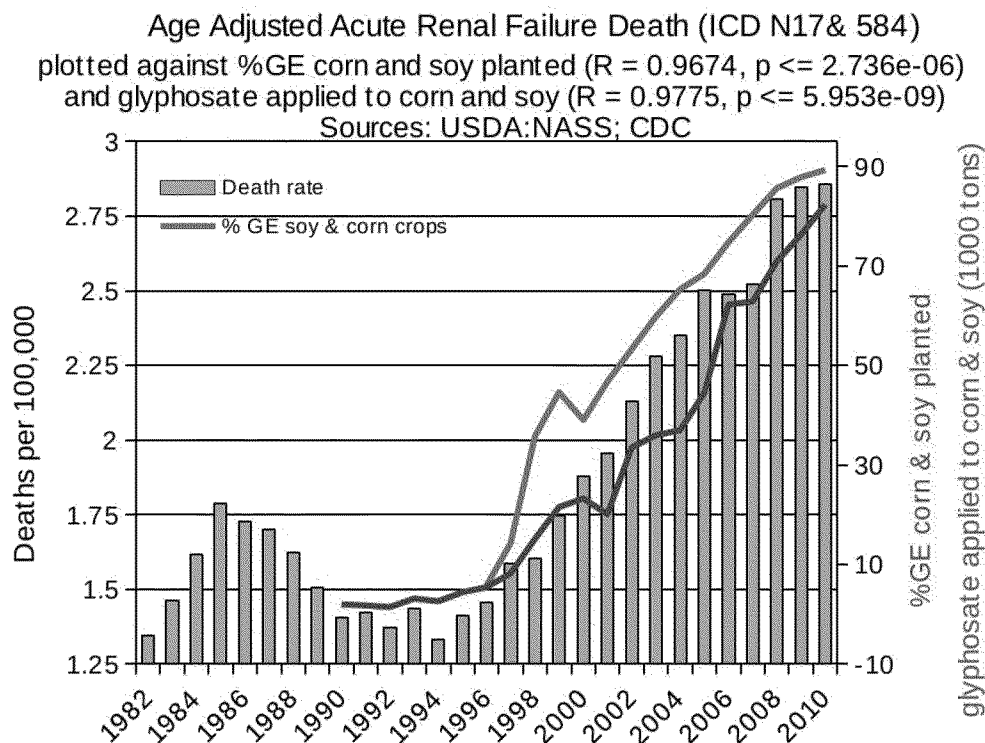
Researchers in Sri Lanka reported massive kidney fa   ilure in rice paddy workers exposed to glyphosate in combination with minerals in hard wat   er. According to Jayasumana et al. (2014) glyphosate's strong chelating properties allow it t   o combine with heavy metals and arsenic in hard water resulting in damage to renal tissues, thereby   causing chronic kidney diseases. The authors concluded that, "The GMA [Glyphosate-metal/arsenic   complex] lattice hypothesis gives rational and consistent explanations to the many observations an   d unanswered questions associated with the mysterious kidney disease in rural Sri Lanka. Furth   ermore, it may explain the similar epidemics of CKDu [Chronic Kidney Disease of Unknown etiology] o   bserved in Andra Pradesh, India and Central America" (p. 2139).

An earlier study found that a 96 hour exposure to l   ow levels of Roundup in water caused oxidative stress to the cells in the kidneys of goldfish (Lus   hchak et al., 2009). Studies by El-Shenawy (2009) and de Liz Oliveira Cavalli et al. (2013) confirm t   hat Roundup and its active ingredient, glyphosate, caused oxidative stress and necrosis in the hepatic cells of rats.

The only lifetime feeding trial of rats with GE maize, Roundup, and GE maize combined with Roundup, compared to the controls fed the non-GE isogenic li   ne of the maize, found very significant chronic kidney deficiencies, for all treatments compared to the controls. Seralini et al. (2014) reported that, "In treated males, liver congestions and necrosis were   2.5 to 5.5 times higher. Marked and severe nephropathies were also generally 1.3 to 2.3 times greater. In females, all treatment groups showed a two- to threefold increase in mortality, and deaths were earlier." (p.1)

Age Adjusted End Stage Renal Disease Deaths
(ICD N18.0 & 585.6)
plotted against %GE corn & soy planted (R = 0.9578, p <= 4.165e-06)
and glyphosate applied to corn & soy (R = 0.9746, p <= 7.244e-09)
Sources: USDA:NASS; CDC

Figure 18. Correlation between age-adjusted End Stage Renal Disease deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Age Adjusted Acute Renal Failure Death (ICD N17 & 584)
plotted against %GE corn and soy planted (R = 0.9674, p <= 2.736e-06)
and glyphosate applied to corn and soy (R = 0.9775, p <= 5.953e-09)
Sources: USDA:NASS; CDC

Figure 19. Correlation between age-adjusted renal failure deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Correlations of gastrointestinal disorders, (inflam matory bowel disease, intestinal infections and liv er disorders) with the planting of GE crops and glyphosate applications
It is well-known that autistic children and people   who suffer from neurological diseases also suffer intestinal problems (Anderson, 2012; Kang, 2013; As   hwood, 2003). According to Samsel & Seneff (2013b), glyphosate also disrupts the gut microbial balance. Data for inflammatory bowel disease were

obtained from the CDC hospital discharge data and a re plotted in Figure 20 (CDC, 2013e). Data for deaths due to intestinal infection were obtained fr om the CDC mortality files (CDC, 2013b) and are shown in Figure 21.

While retrieving these data, we stumbled upon a sta   rtling increase in hospital discharges for viral hepatitis C. At first this was puzzling. We do not imply that hepatitis is transmitted by food, but th at the CaMV is very similar to hepatitis and HIV and if th ose are already dormant in the body, introduction o f the CaMV through the food could activate them. Ho (2013, p. 4760) has stated that, "insertion mutations [can occur] including those leading to ca   ncer, activation of dormant viruses, and recombination with viral sequences in the genome to   generate new viruses; all of which have been demonstrated in gene therapy experiments". And also , "New evidence raises the possibility that the CaMV 35S promoter in practically all transgenic crops grown commercially may enhance multiplication of disease-associated viruses including HIV through   induction of proteins required for their transcription" (Ho et al., 2009, p. 172).

Furthermore, recent evidence (Furuta, 2013) suggest s that cholesterol sulfate is an inhibitor of the hepatitis C virus and, according to Samsel & Seneff   (2013a), glyphosate also interferes with the uptake of nutrients, particularly sulfates. We sear   ched the hospital discharge data from the CDC (CDC, 2013e) for diagnoses of hepatitis C. We found   a correlation between those data and the percent of GE soy crops planted in the US. Results   are shown in Figure 22. We also looked at the data for deaths from HIV, but found that they have been steadily decreasing.

Hospital discharge diagnoses (any) of Inflammatory Bowel disease
(Crohn's and Ulcerative Colitis ICD 555 & 556)

plotted against glyphosate applied to corn & soy (R = 0.9378, p <= 7.068e-08)
Sources: USDA & CDC
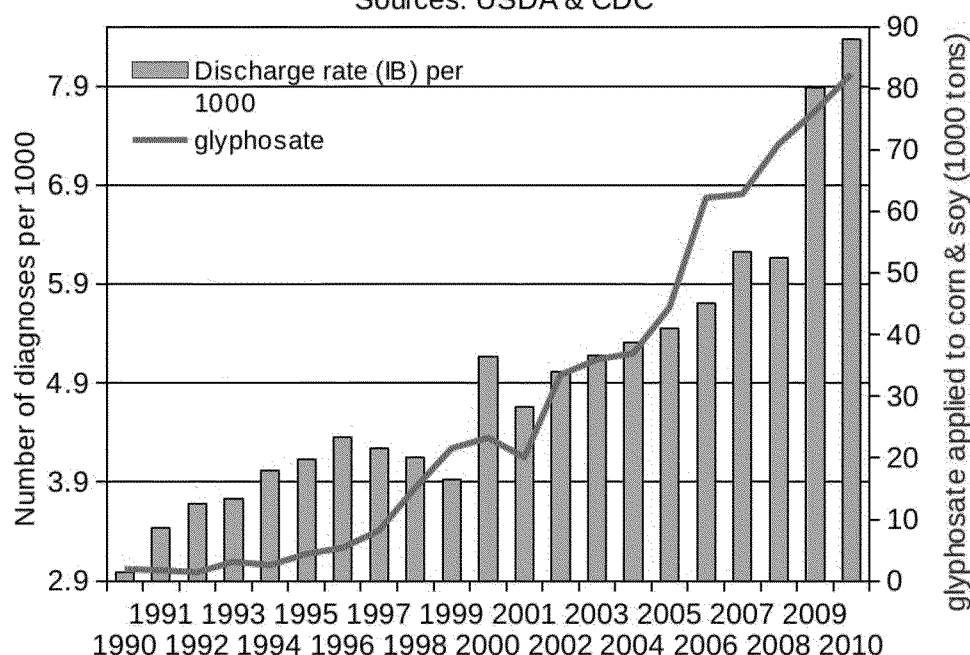
Figure 20. Correlation between inflammatory bowel disease and glyphosate applications to US corn and soy crops.

25

Age Adjusted Deaths due to Intestinal Infection
(ICD A04, A09; 008, 009)
plotted against glyphosate applied to corn & soy (R = 0.9738, p <= 7.632e-09)
Sources USDA:NASS; CDC

Figure 21. Correlation between age-adjusted intestinal infection deaths and glyphosate applications to US corn and soy crops.

(ICD 070.4-070.7)
plotted against % acres planted in GE soy
(R = 0.9456, p <= 6.914e-06)

Figure 22. Correlation between diagnoses of hepatitis C and GE soy crop growth.

Correlations of neurological disorders (autism, Alz heimer's, senile dementia and Parkinson's) with the planting of GE crops and glyphosate applications

The incidence and prevalence of neurological disorders are not readily available for two reasons: they are not as well-studied as other diseases (cancer,   diabetes etc.), and the diagnostic methods keep changing. Researchers argue over whether the increa   ses are real, or a by-product of changes in diagnostics, along with greater attention given to   these disorders in recent times. For example, a former diagnosis of mental retardation might now result in a diagnosis of autism. Furthermore, there is a large degree of overlap in symptoms. Typical mani   festations of ADHD, such as distractibility or hyperactivity, are also present in pediatric bipola   r disorder. However, the increases have been so

great in recent years that most experts now agree t   hat they are real and must be environmentally induced (Weintraub, 2011).

We found data for autism from the US Department of Education, Individuals with Disabilities Education Act (USDE:IDEA) (Gallup, 2002; Snyder, 2012). These   data are for autistic children 6-21 years old served under IDEA. In the plot in Figure 23, the nu mbers for the year correspond to the beginning of the school year in the fall.

According to the University of Washington Institute   for Health Metrics and Evaluation (UW, 2012), Alzheimer's disease went from number 32 in 1990 to   number 9 in 2010 in the ranking of leading causes of premature death in the US. Senile dementia and its care costs have also skyrocketed in the last two decades. Prevalence and incidence data were sparse, but data on death rates were available from 1979. Death data were again obtained from the   CDC for senile dementia, Parkinson's & Alzheimer's diseases (CDC, 2013b). These are presen ted in Figures 24-26. A weaker correlation was found for multiple sclerosis deaths (*R* = 0.88 for %GE crops and *R* = 0.83 for glyphosate applications).

Cattani et al. (2014) found that both acute and chr onic exposure to Roundup induced oxidative stress resulting in neural cell death and neurotoxic effec ts in the hippocampus of immature rats. Lushchak et al. (2009) found that a 96-hour exposure to low lev els of Roundup in water caused oxidative stress to the cells in the brains, livers and kidneys of goldfish.
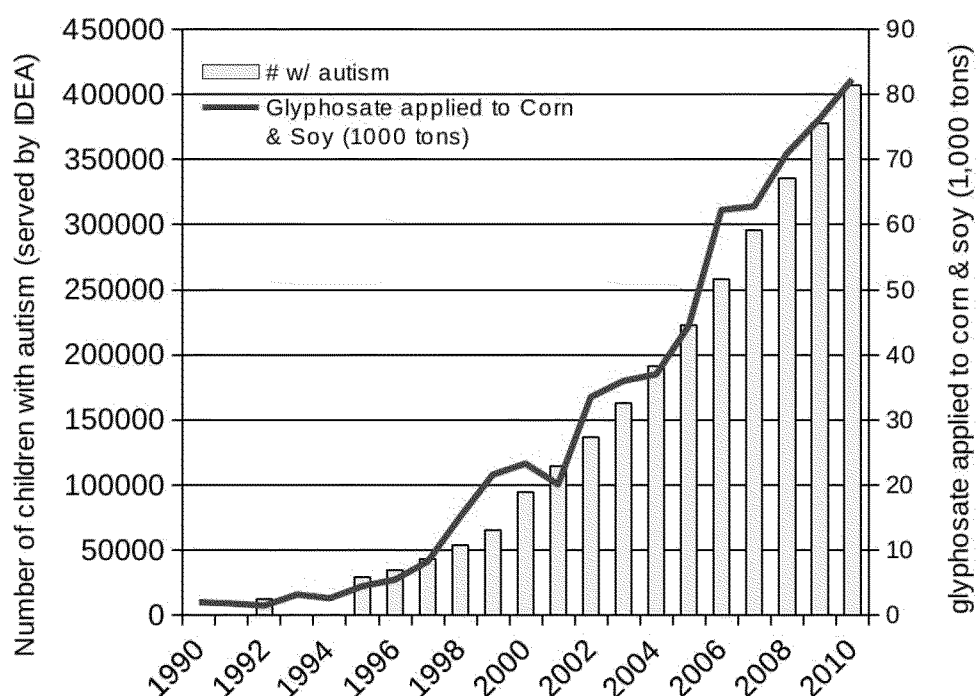
Figure 23. Correlation between children with autism and glyphosate applications.

Age Adjusted Deaths from Senile Dementia
(ICD F01, F03 & 290)

Plotted against glyphosate use on corn & soy
(R = 0.9942, p <= 1.822e-09)
Sources: USDA:NASS; CDC
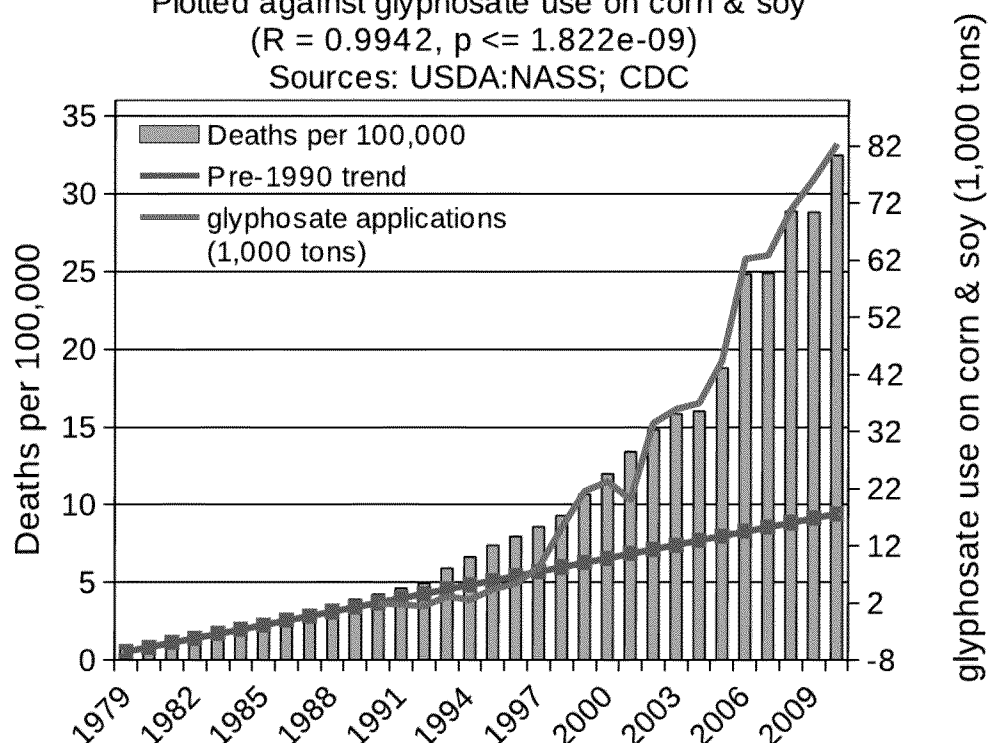
Figure 24. Correlation between age-adjusted dementia deaths and glyphosate applications.

Age Adjusted Deaths from Alzheimer's (ICD G30.9 & 331.0)

Plotted against glyphosate use (R = 0.917, p <= 2.205e-07) &
%GE crops planted (R = 0.9373, p <= 9.604e-06)
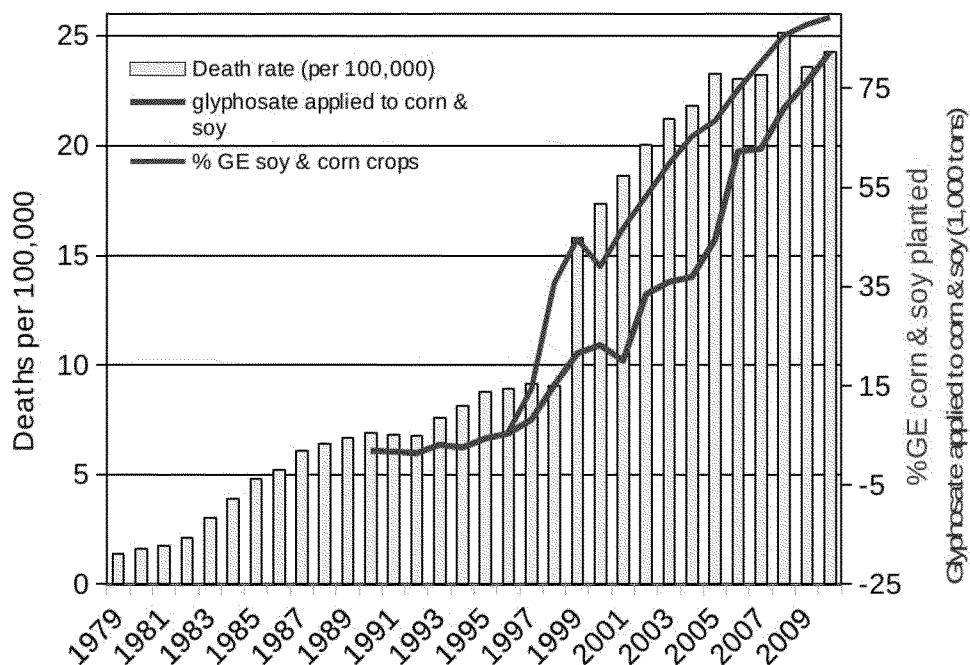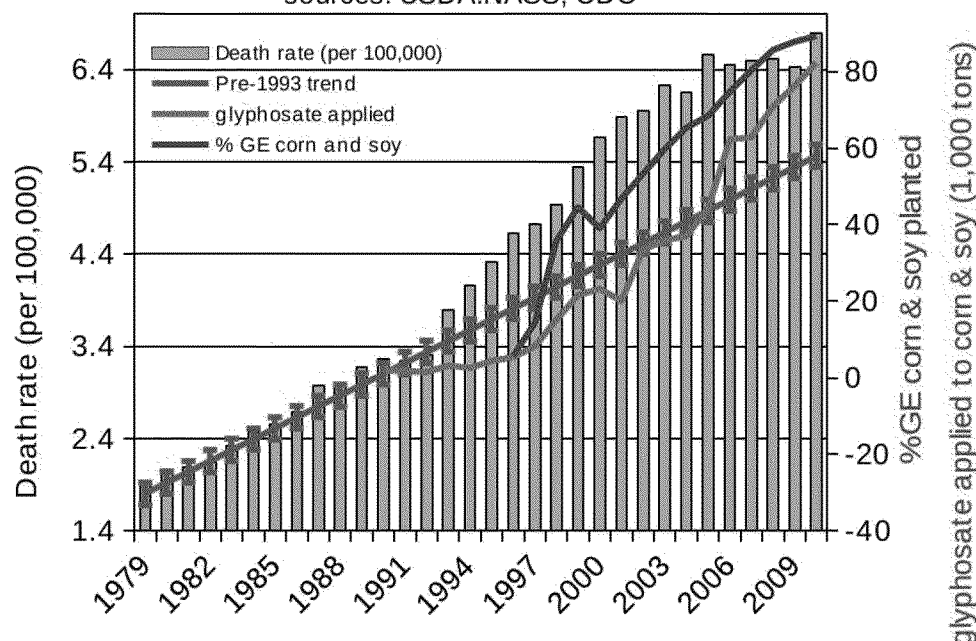sources: USDA:NASS; CDC

Figure 25. Correlation between age-adjusted Alzheimer's disease deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Age Adjusted Deaths from Parkinson's disease
(ICD G20 & 332.0)
plotted against glyphosate use on corn & soy (R = 0.8754, p <= 1.631e-06)
and percent GE corn & soy planted (R = 0.9516, p <= 5.398e-06)
sources: USDA:NASS; CDC

Figure 26. Correlation between age-adjusted Parkinson's disease deaths and glyphosate applications and percentage of US corn and soy crops that are GE.

Statistical summary of disease data correlations with GE crops planted and glyphosate applications
The Pearson correlation coefficient is a measure of the linear relation between two variables, X and Y. The correlation coefficient, R lies between -1 and 1, and the coefficient of dete   rmination, R^2 is the proportion of the variation in Y that can be accounted for by the linear part of it s relation with X. If, for example, $R = 0.9$, then 81% of the variation in Y can be accounted for by the linear relation with X. If R = 1 and the (x,y) pairs are plotted on a graph, they lie on a straight line. In the social sciences, $R \geq 0.8$ is considered a strong correlation. The values obtained here are much greater than that.

It is important to bear in mind that the correlatio n coefficient measures only the strength of the lin ear part of the relation. Correlation of course only su   ggests cause and effect; it does not prove it. If, however, the variables X and Y both increase in time but not linearly, then the o   bservation that the relation between them is close to linear, as indicated by the very high correlation coefficients that were obtained, is stronger evidence in favour of a causal relationship.

The correlation coefficients, their squares and the p-values for the various incidences, prevalence an d deaths due to diseases are summarised in Tables 3 and 4.

Table 3. Pearson's coefficients between disease and glyphosate applications (N=21 encompassing 1990-2010), except autism (N=16; autism data only available for 1995-2010).

Disease	Coefficient, R	$R^2 \times 100$	Probability, p
Thyroid cancer (incidence)	0.988	97.6	≤7.6E-9
Liver cancer (incidence)	0.960	92.1	≤4.6E-8
Bladder cancer (deaths)	0.981	96.2	≤4.7E-9
Pancreatic cancer (incidence)	0.918	84.2	≤4.6E-7
Kidney cancer (incidence)	0.973	94.8	≤2.0E-8
Myeloid leukaemia (deaths)	0.878	77.1	≤1.5E-6
Lipoprotein metabolism (deaths)	0.973	94.8	≤7.9E-9
Hypertension (deaths)	0.923	85.2	≤1.6E-7
Stroke (deaths)	0.925	85.5	≤1.5E-7
Obesity	0.962	92.5	≤1.7E-8
Diabetes (prevalence)	0.971	94.3	≤9.2E-9
Diabetes (incidence)	0.935	87.4	≤8.3E-8
ESRD (deaths)	0.975	95.0	≤7.2E-9
Renal failure (deaths)	0.978	95.6	≤6.0E-9
Autism (prevalence)	0.989	97.9	≤3.6E-7
Alzheimer's (deaths)	0.917	84.1	≤2.2E-7
Parkinson's (deaths)	0.875	76.6	≤1.6E-6
Dementia (deaths)	0.994	98.8	≤1.8E-9
Multiple sclerosis (deaths)	0.828	68.5	≤1.1E-5
Intestinal infection (deaths)	0.974	94.8	≤7.6E-9
Inflammatory bowel	0.938	88.0	≤7.1E-8

Table 4. Pearson's coefficients between disease and the percentage of US corn and soy crops that are GE (N=15 encompassing 1996-2010; GE crops were first planted in 1995).

Disease	Coefficient, R	$R^2 \times 100$	Probability, p
Thyroid cancer (incidence)	0.938	87.9	≤2.2E-5
Liver cancer (incidence)	0.911	82.9	≤5.4E-5
Bladder cancer (incidence)	0.945	89.3	≤7.1E-6
Pancreatic cancer (incidence)	0.841	70.7	≤4.0E-4
Kidney cancer (incidence)	0.940	88.4	≤2.0E-5
Myeloid leukaemia (deaths)	0.889	79.0	≤5.4E-5
Lipoprotein metabolism (deaths)	0.955	91.2	≤4.7E-6
Hypertension (deaths)	0.961	92.3	≤3.7E-6
Stroke (deaths)	0.983	96.6	≤1.4E-6
Obesity	0.962	92.5	≤3.5E-6
Diabetes (prevalence)	0.983	96.6	≤5.1E-7
Diabetes (incidence)	0.955	91.2	≤2.0E-6
ESRD (deaths)	0.958	91.7	≤4.2E-6
Renal failure (deaths)	0.967	93.6	≤2.7E-6
Alzheimer's (deaths)	0.937	87.9	≤9.6E-6
Parkinson's (deaths)	0.952	90.6	≤5.4E-6
Multiple sclerosis (deaths)	0.876	76.7	≤8.0E-5
Hepatitis C (hospital diagnoses)	0.946	89.4	≤6.9E-6

There are four diseases in Table 3 that are not in   Table 4 because we did not plot the percentage of GE crops for autism, dementia, inflammatory bowel a   nd intestinal infection. We plotted only glyphosate applications against inflammatory bowel   and intestinal infection because the information from Samsel & Seneff (2013b) indicated that glyphos   ate causes intestinal problems by killing beneficial bacteria in the intestines. We plotted o   nly glyphosate applications against autism and dementia because the correlation coefficients were already 0.989 and 0.994 respectively.

There is one disease (hepatitis C) in Table 4 that   is not included in Table 3 because we did not plot hepatitis against glyphosate applications. This is   because, according to Ho (2009; 2013), viral diseases may be activated by the CaMV promoter used   in GE crops. We plotted the hepatitis C against the percentage of GE soy crops planted in t he US because soy was more quickly adopted, is currently 98% of the total US soy crops, and is ubiquitous in packaged food in the US.

Table 5 provides a summary of which diseases have t he highest correlation. All of these have a very strong correlation coefficient with very high signi   ficance (very low probability that the correlation   is random). The highest correlations were found for se nile dementia, autism, bladder and thyroid cancer with glyphosate applications and stroke and diabete s prevalence with %GE crops planted. In most cases, diseases that had correlation coefficients o f less than 0.95 with glyphosate applications had greater than 0.95 with %GE crops planted and vice-v   ersa. Some had correlation coefficients exceeding 0.95 for both GE crops and glyphosate app   lications: obesity, lipoprotein metabolism disorder, ESRD, renal failure, prevalence of diabetes as well as kidney and bladder cancers.

Table 5. Summary of correlation coefficients, showing the number of diseases with *R* in the various ranges for glyphosate applications and for %GE crops planted.

R-value range	Correlation with glyphosate	Correlation with %GE crops planted
	No. Disease	No. Disease
$R > 0.98$ $R^2 \times 100 > 96\%$	4 Thyroid, autism, dementia, & bladder	2 Stroke, diabetes (prevalence)
$0.97 < R < 0.98$ $94\% < R^2 \times 100 < 96\%$	6 ESRD, diabetes (prevalence), lipoprotein metabolism, intestinal, kidney & renal	
$0.95 < R < 0.97$ $90\% < R^2 \times 100 < 94\%$	2 Obesity, liver	7 Parkinson's, hypertension, diabetes (incidence), obesity, lipoprotein metabolism, ESRD, renal
$0.90 < R < 0.95$ $81\% < R^2 \times 100 < 90\%$	6 Diabetes (incidence), inflammatory bowel, hypertension, stroke, Alzheimer's, pancreatic	7 Liver, bladder, kidney thyroid, pancreatic, Alzheimer's, hepatitis
$0.86 < R < 0.9$ $74\% < R^2 \times 100 < 81\%$	2 Parkinson's, myeloid leukaemia	2 Myeloid leukaemia, multiple sclerosis
Correlation ≥ 0.90	18	16

Interpretation of results
Some of the plots show a significant linear rise th at began prior to 1990. Others show a peak in the 1980s, then a decline followed by another rise in t   he 1990s. Clearly, there are multiple factors involved. Though the data for glyphosate are only a vailable beginning in 1990, glyphosate was first introduced in the marketplace in 1974. Other known endocrine disruptors are: BPA (bisphenol-A) and phthalates (both in plastics), dioxins (by-product   of smelting, paper bleaching, manufacture of herbicides and pesticides), hexane (cooking oil ext   raction), atrazine, and polychlorinated biphenyls (PCBs - used in electrical equipment, coatings, ink   s, adhesives, flame-retardants, and paints) (Kavlock, 1996).

The population of the US is bombarded with a verita   ble cocktail of chemicals daily in addition to GE food and glyphosate (Reuben, 2010). These include f   ood preservatives (BHA & BHT), water contaminants (chlorine & fluoride), heavy metals, f ood additives (aspartame, monosodium glutamate, carrageenan) and food colouring, to name a few. The   US President's Cancer Panel reported that a study by the CDC found many toxic chemicals in the   blood and urine of most Americans that they tested, and the Environmental Working Group found u p to 232 xenobiotic chemicals in the placental cord blood of newborns in the US (Reuben, 2010). Th   e people have been exposed to an increasing background level of chemicals and other toxins for   over 70 years, yet few, if any, have increased at the rate of glyphosate and GE crops.

According to Samsel & Seneff (2013a), glyphosate disrupts the ability of animals, including humans, to detoxify xenobiotics. This means that exposures to   the numerous chemicals in food and the environment, such as endocrine disrupting chemicals   and carcinogens, could be causing levels of damage that would not occur if the body were able to detoxify them. The accumulation of toxins as the result of low levels of poisoning over a long perio d of time leads to a high body burden or toxic load . Every person is unique and the ability of the body, or the path it takes to detoxify, is both genetic and acquired (Anderson, 2012). If the body burden becom es overwhelming, it could be that only a small amount of additional stress will induce the breakdo wn of the system in whatever way that manifests according to individual predisposition.

If we know that a causal factor exists, that is A c   auses B, then we would expect a high degree of correlation between the two data sets for A and B. The inverse is not true, i.e. because there is a hi gh degree of correlation between A and B it is not necessarily the case that A causes B or vice-versa.

However, we have data for 22 diseases, all with a h   igh degree of correlation and very high significance. It seems highly unlikely that all of   these can be random coincidence. Ruling out coincidence, we are left with these three options:
1. There is a direct cause and effect relationship
2. The relationship may be caused by a third variable
3. The relationship may be caused by complex interactions of several variables

In 1965, Austin Bradford Hill addressed the problem of deducing causation when observations reveal an association beyond what can be considered random   chance (Hill, 1965). Hill proposed nine conditions that should be considered as an aid in d   etermining causation. These are the well-known Hill's Criteria. Since we have not performed an exp   eriment, and we do not have information on dose/response, it would be difficult to go through and say this criterion is true and this one is not for all of the diseases as a whole. However, we quote from   the American Academy of Environmental Medicine's position paper on genetically modified (GM) foods: "[S]everal animal studies indicate serious health risks associated with GM food consum ption including infertility, immune dysregulation, accelerated aging, dysregulation of genes associated with cholesterol synthesis, insulin regulation, cell signaling, and protein formation, and changes in the liver, kidney, spleen and gastrointestinal system." "There is more than a casual association between GM   foods and adverse health effects. There is causation as defined by Hill's Criteria in the area s of strength of association, consistency, specific ity, biological gradient, and biological plausibility" (Dean & Armstrong, 2009, online). The document goes on to explain in detail why and how each of these criteria are met based on published research.

Conclusions

These data show very strong and highly significant   correlations between the increasing use of glyphosate, GE crop growth and the increase in a mu   ltitude of diseases. Many of the graphs show sudden increases in the rates of diseases in the mi   d-1990s that coincide with the commercial production of GE crops. The large increase in glyph osate use in the US is mostly due to the increase in glyphosate-resistant GE crops.

The probabilities in the graphs and tables show tha   t it is highly unlikely that the correlations are a coincidence. The strength of the correlations shows that there is a very strong probability that they are linked somehow. The number of graphs with similar data trends also indicates a strong probability that there is a link. Although correlation does not necessarily mean causation, when correlation coefficients of over 0.95 (with *p*-value significance levels less than 0.00001) are c alculated for a list of diseases that can be directly linked to glyphosate, via its known biological effects, it would be imprudent not to consider causation as a plausible explanation.

We do not imply that all of these diseases have a s   ingle cause as there are many toxic substances and pathogens that can contribute to chronic diseas e. However, no toxic substance has increased in ubiquity in the last 20 years as glyphosate has. Th   e disruption by glyphosate of the detoxification pathways in the human body can intensify the effect   of other toxic chemicals. The disruption of the Cytochrome P450 pathways by glyphosate could account for it causing numerous diseases (Samsel & Seneff, 2013a). The Cytochrome P450 enzymes are the superfamily of enzymes that are responsible for around 75% of the reactions involved in drug me   tabolism and the oxidation of organic molecules (Guengerich, 2008). Another critical issue is that glyphosate is an endocrine disruptor and it has bee n argued that there are no safe levels of endocrine d isruptors (Vandenberg et al., 2012; Bergman et al., 2013). This would imply that the current permitted   residue levels in food could be causing multiple

health problems that have been documented in the sc   ientific literature to be caused by endocrine disrupting chemicals.

The findings reported by Kruger et al. (2014) that   there is no significant difference in glyphosate residues detected in the urine, tissue and organs of cows is evidence that glyphosate bio-accumulates in our bodies. The research showing that Roundup an d glyphosate cause oxidative stress resulting in changes to cell functions, necrosis in cells and ne   urotoxic effects in brain, kidney hepatic, testis a nd Sertoli cells needs to be considered as a possible   causative agent in a range of diseases (Cattani et al., 2014; de Liz Oliveira Cavalli et al., 2013; Lushchak et al., 2009; El-Shenawy, 2009).

The prevalence of certain diseases is likely to ris e simply due to better treatments available, allowi ng people to live longer with the diseases. All of the   graphs, save three (inflammatory bowel, hepatitis & autism), are age-adjusted. The age-adjustment would   partially account for many of the people living longer with chronic diseases, and consequently this group of people would not be a significant reason for the dramatic increase in diseases found in most of the graphs.

An increase in surveillance of a particular disease   can artificially increase the prevalence of the disease because it merely increases the known numbe r of cases, when the actual number has not changed. Surveillance of certain diseases has been   boosted over recent decades, and may have artificially increased the prevalence of some of th   ese diseases. The increased surveillance would initially find more cases and subsequently show an   increase; however this would be expected to capture approximately the same percentage every yea r and would thus level off fairly quickly. If the actual prevalence of diseases was not increasing, t   he graphs would show a new stasis that would remain fairly level reflecting the extra cases found by the surveillance. The rates of disease prevalence are steadily increasing, so increased surveillance cannot be a significant reason for the dramatic and continuing rise in many of the diseases shown in th   e graphs since the 1990s. Any increase in surveillance could only account for part of the increase shown in the graphs.

In reviewing the toxicity of chemicals based on the   latest peer reviewed science, the US President's Cancer Panel report was critical about the current testing methodologies and the lack of action taken by regulatory authorities (Reuben, 2010). According to the report, the regulatory approach in the US is reactionary rather than precautionary. Instead of t   aking preventive action when uncertainty exists about the potential harm a chemical or other environmental contaminant may cause, a hazard must be incontrovertibly demonstrated before action is initiated. Instead of requiring industry to prove the safety of their devices or chemical products, the public b   ears the burden of proving that a given environmental exposure is harmful.

The current testing methodologies, length of feed t   rials of GE crops, and the parameters measured are insufficient to evaluate the health problems th   at may be caused by diets consisting of GE food (Seralini et al., 2011). The lack of proper testing protocols means that there is insufficient data to show that the increase in GE crops and glyphosate is not   linked to the increase in diseases. The data presented in this paper highlight the need for inde   pendent scientific research to be conducted, especially in the areas of the endocrine disruption , cancer precursor, oxidative stress, gut microbiom e and the Cytochrome P450 pathways. It is our hope that, in addition to more basic research in the form of toxicology and carcinogenic studies, epidemiolog y studies will be undertaken by experts in each of these disease categories.

Conflicts of Interest
The authors declare no conflicts of interest.

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